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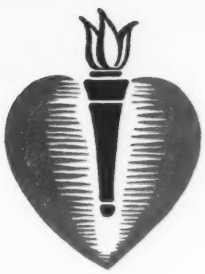

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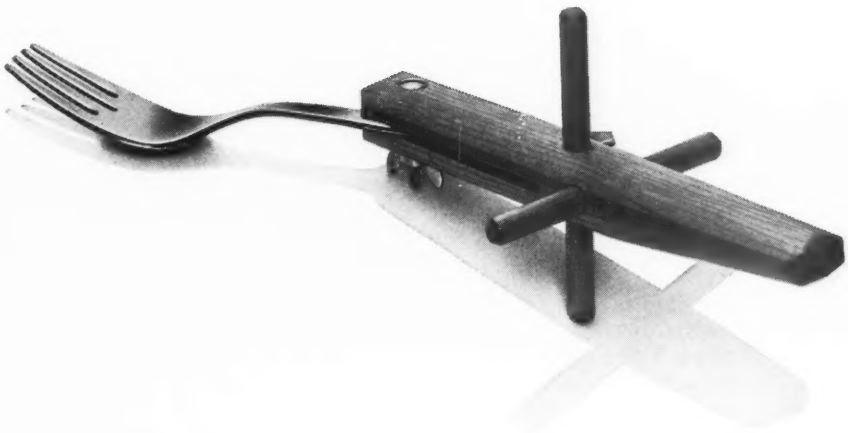

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# Editorial

## Non-Destructive Testing

*By* CHARLES T. DOTTER, M.D.

UNDER the unprecedented stimulus of nuclear weapons testing, recent public and scientific attention has been focused on the biological significance of radiation. At first, the principal concern was with fallout but it soon became apparent that the dosage associated with medical radiation was approximately 30 or 40 times greater, accounting for roughly a third of the radiation received by the average individual during the first 30 years of life. Thus, to the extent that radiation hazard exists, it is clearly an important responsibility of the medical profession.

### BIOLOGICAL EFFECTS OF X-RAYS

Our ability to obtain a radiograph or fluoroscopic image depends upon the absorption of part of the x-ray beam by the object being examined. If this happens to be a metal casting, no noticeable change takes place, and it is probably correct to look upon this use of x-rays as nondestructive testing. When—as happens over 25 million times each year in this country—the x-ray beam loses energy to healthy tissue cells, it invariably causes damage even though, as in shaving, the damage is usually invisible and negligible. Since x-rays scatter within tissues and since they possess great penetrating power, they are able to inflict cell damage at considerable distance from the primary beam. Most scattered x-rays produce relatively little damage in that for every cellular catastrophe they cause, there are billions of healthy cells. When the rays damage critical genetic material in gonadal tissue, the direct result is similar—imperceptible somatic change; but this change, known as a mutant, may become highly significant. There is probably no threshold level of exposure below which it could not occur. When such a mutation takes place in the genetic material of a cell which later manages to fulfill its intended function, the damage becomes applicable to the health of the population rather than to that of a few cells, an organ system or the individual.

From the Department of Radiology, University of Oregon Medical School, Portland, Ore.

### *Somatic Damage*

The exposures required for ordinary diagnostic radiology are relatively small—in fact they are incapable of producing noticeable deleterious effect upon the individual and highly unlikely to produce gonadal changes of subsequent importance. At present, it is only through ignorance or carelessness, comparable to cutting one's jugular vein while shaving, that diagnostic procedures ever cause grossly evident damage to patient or physician. The term "martyr" no more belongs to the injured pioneer radiation worker than to the bleeding child with a razor blade. Thanks to the former, we already know the somatic effects of radiation on man and have set up the genetic experiment at a human level. Our knowledge is now at the point where leukemia can no longer be considered an occupational hazard of radiologists for we know enough to protect ourselves and our patients. Thoroughly trained in the need and technics for protecting himself, today's radi-

ology resident is less apt to die of leukemia than residents on other services. If anyone is so mistaken as to think that protective measures just won't work, consider the fact that personnel cruising on the Nautilus live constantly in close proximity to a nuclear reactor, yet by measurement receive less exposure to radiation than do those who stay behind! So much for the ordinary sort of somatic damage. That it still occurs in connection with the use of diagnostic x-rays is, of course, inexcusable.

*Genetic Complications*

When x-rays reach the gonads, they are capable of causing mutations in the genetic material of the individual. Mutants are simply random changes. Though mutations allowed our evolutionary ascent from the Paleozoic slime, mutations are nonetheless undesirable by a ratio of perhaps 1000:1. There are other causes of mutation than radiation. Heat is said to be one of them. Regardless of how it is caused, mutation is undetectable at the time of its occurrence. It is never significant unless the damaged genetic material subsequently plays a role in the formation of offspring. Even then, it usually would not be evident since most mutations are recessive in type. Should circumstances allow the passage of an altered gene through succeeding generations, the chances are that eventually it will meet another similarly located recessive mutant gene and thereby cause some sort of change in the endowed individual. This might turn out to be premature baldness, an atrioventricularis communis, or the tendency to contract rheumatic fever. When the change is incompatible with life, the mutation is spoken of as lethal. The odds against the occurrence of any given sequence of events are about as slim as the chain of coincidence leading any of us to some particular place at a given point in time—and yet, of course, everyone is somewhere.

Thus, as far as we know, any radiation reaching the gonads can produce an increase in the mutation rate—the less radiation that gets there, the less is the likelihood of mutation. Geneticists believe that the relationship is linear. Everyone who knows much about it agrees that—other things being equal—the proper course of action is to keep the exposure as low as possible. This is the central point at issue in a major controversy over the advisability of nuclear weapons testing. Scientist, politician, newspaper writer, housewife—all seem willing to choose sides in an all-black or all-white approach. Those who would deny its importance argue that there is no proved example of an x-ray-induced mutation in man. This may or may not be true; in either event, it isn't very meaningful since the widespread use of x-rays is a relatively recent development. There are few biological theories more soundly established than the basic precepts of genetics. Furthermore, there is no good reason to believe that man is genetically different from other animals in this particular respect. No doubt during the fury of debate a well-known radiologist was heard to observe that "There have been over two full generations since the discovery of x-rays, yet our hereditary make-up has not undergone a striking or sudden change for the worse." One wonders if he has discovered some handy means for running a quick check on chromosomes (other than through the observation of several generations of grandchildren yet to be conceived). Next time you are told we know very little about the biological effects of radiation, remember that there are few areas in modern biological science where we know as much. Viewed at close range, controversy often seems to be a conflict of extremes; its resolution is usually a matter of balance. The practicing physician's knowledge of familial disease strengthens his respect for genetic mechanisms while his clinical experience gives him daily proof of the indispensable role of x-rays in the practice of medicine. Consequently he is not likely to go overboard in either direction, and it is fortunate that the decision as to when and how medical x-rays are to be made is his. All physicians are morally obligated to give the matter some serious thought.

Certain geneticists have overstated the ca-

against radiation. They can hardly be blamed when it is noted that the medical profession as a whole has only recently begun to pay serious attention to what they have been saying for the last 20 years. Paradoxically, congressional investigations, biased journalism, and heightened public interest seem to have had a more profound effect than did the atom bomb or Dr. Müller's 1946 Nobel prize-winning research, which established the fact that x-rays cause inheritable disease. Perhaps after 2 decades of frustration the geneticists have given up writing on walls in favor of the numbers' game. Their motives are better than their numbers which add up to a unilateral statistical appraisal of the effect on mankind of radiation-induced hereditary defects. The mathematical calculations are no doubt accurate but, lacking comparable analysis of favorable consequences, the derived data are less likely to lead to useful scientific conclusions about radiation than to highly effective propaganda.

Radiologists agree that the somatic and genetic effects of ionizing radiation represent a calculated risk of their specialty. It happens that these risks may be minimized. Knowledge and skill applied in selecting patients and performing x-ray examinations bear a direct relationship to the risk involved. If the observed complications of radiology are in any sense a guide to its hazards, the specialty is relatively benign compared to virtually all other fields of medical practice. In this connection overirradiation is not in the same category as a postoperative wound infection, since the infection is a complication or legitimate risk accepted by the patient undergoing surgery while overirradiation is nearly always a product of ignorance in the face of available knowledge. In certain instances it can have far more serious effects. The untrained, incompetent user of x-rays is not likely to be recognized as such by his patients or colleagues, unlike the inept surgeon venturing beyond his limitations. There is no radiologic counterpart of the tissue committee. Operations are done in hospitals, medications are usually a matter of record, but each year literally several million x-ray examinations are done routinely in the offices of men some of whom have little grasp of the basic principles of radiation safety. This is not a quarrel with the right of the entire medical profession to make use of x-rays. All of us have and should retain that right. It is, rather, a strong denial that right exists in the absence of competency. There is a better alternative to legislative or regulatory control of the medical use of x-rays, and that is professional excellence. In its interest there follow some crude but realistic suggestions bearing mostly upon the use of x-rays in medicine:

In each case, review the indications for x-ray examination or therapy just as you would for digitalization or surgery. Do routine check-up studies sparingly, particularly in young patients. Avoid requesting or giving radiation therapy in the absence of malignancy. Be certain you are not using radiologic diagnosis just to convince your patient that nothing was overlooked in the study of his case. Don't do check-up routines that include a "GI series, colon, gallbladder and IVP" unless you're also thinking of throwing in a laparotomy "just to be sure while the patient's in the hospital anyway." Don't let prepaid medical care and hospitalization programs influence your practice of medicine, especially your decision as to the x-ray or laboratory studies you order. Money never was an indication for these. Shooting the works boosts the cost of medical care while lowering its standards. Don't substitute routine diagnostic work-ups for individual thought. This applies to blood counts, blood tests, blood chemistries, to BMR's, EKG's—even to autopsies—just as surely as it applies to a routine GI series.

Finally, here are a few questions for those who use their own x-ray equipment. The questions should give some idea as to whether it is being used to best advantage.

Are you one of the more than 50,000 non-radiologist physicians who uses x-ray equipment? What's the output of your fluoroscope? How many millimeters of aluminum are in the beam? (If there is no filter or if you don't know, you ought to look into it. Filtration provides a good way of minimizing exposure.) Do you always dark-adapt 20 minutes before fluoroscoping patients? At fluoroscopy do you always wear gloves and an apron? Does your technician have proper protection? Has your technician received adequate training in x-ray technic? Do you use

gonadal shielding? Is the beam always limited to the area being examined? (This is important.) Do you frequently have to repeat examinations because of faulty technic? Are your processing solutions changed regularly? Are you taking advantage of new developments in the field? (If you haven't changed your procedure in a year, you're not. If you haven't changed it in five years, you might give thought to selling the apparatus and sending your patients to a radiologist.) Are you sure you checked all the ribs on the last chest film you read—osteolytic metastases begin small. Do you fluoroscope? If you do, is there a timing clock on the control? Can the screen be moved without moving the tube—it shouldn't. Do you fluoroscope with the shutters wide open? Do you have "staccato foot" so that your fluoroscopy sounds like a machine gun? Do you have the right filters and cones? Did you know that the radiation exposure during a one-minute chest fluoroscopy is often the equivalent of 100 or more 14 × 17 chest films?

Undoubtedly, most of America's doctors have long been aware of both the favorable and the undesirable consequences of radiation exposure. Radiology has come to be associated with symbols of radiation safety as the lead aprons and red goggles. Unfortunately, there will probably always be a few thousand physicians who use x-rays to the disadvantage of their patients, the good name of medicine, our future population, and themselves. It is appropriate to close with the words of the Chairman of the National Committee on Radiation Protection, Dr. Lauriston S. Taylor, who summarizes our present problem in 3 short sentences . . .

*"No radiation, other than for the treatment of disease, is known to be beneficial to man. Any radiation exposure received by man must be accepted as harmful. Therefore, the objective should be to keep man's exposure as low as possible and yet, at the same time, not discontinue the use of radiation altogether."*

CHARLES T. DOTTER

**Thal, A. P., Lester, R. G., Richards, L. S., and Murray, M. J.: Coronary Arteriography in Arteriosclerotic Disease of the Heart.** Surg., Gynec. & Obst. **105**: 457 (Oct.), 1957.

In 15 patients of various ages, 5 of whom were thought to have coronary artery disease, the coronary artery system was visualized on serial roentgenograms following the rapid injection of 40 ml. of renografin through a catheter inserted into the ascending aorta, 5 cm. above the sinus of Valsalva. During the injection both carotid arteries were compressed in order to divert the renografin from the brain, and no patient had a serious untoward reaction from the study. Coronary occlusions, narrowings, dilatations, and 1 cardiopulmonary branch were demonstrated with accuracy, later verified at surgery or at autopsy in some instances. The potential usefulness of this technic in studying the natural history of coronary artery disease and in evaluating some patients for cardiac surgery is emphasized.

ROGERS

# Observations on the Delayed First Heart Sound in Mitral Stenosis and Hypertension

*By* ARNOLD M. WEISSLER, M.D., JAMES J. LEONARD, M.D., AND JAMES V. WARREN, M.D.

The measurement of the time between the onset of ventricular depolarization and the first heart sound, the Q-1 interval, has been employed in the phonocardiographic evaluation of patients with rheumatic heart disease. Prolongation of this interval has been noted frequently in patients with mitral stenosis and may be used as evidence in weighing the advisability of operation. In the present study, delayed appearance of the first heart sound was often noted in patients with hypertensive vascular disease as well. The mechanism for these changes as well as their significance in the phonocardiographic evaluation of patients with combined valvular disease and hypertension is discussed.

DELAYED appearance of the first heart sound was originally described in 1911 by Weiss and Joachim as a phonocardiographic sign of mitral stenosis.[1] With the advent of valvular surgery and the consequent need for more accurate assessment of mitral stenosis, interest in this observation has been renewed.[2-8] The measurement of the Q-1 interval, that is the interval between the onset of ventricular depolarization and the first heart sound has been accordingly evaluated as an index of the severity of stenosis. Recent observations in this laboratory have suggested that, in addition, the timing of the first heart sound may be altered in patients with hypertensive vascular disease.[9] The present study was undertaken to gain further information regarding this phenomenon.

## METHOD

Simultaneous logarithmic phonocardiograms and electrocardiograms were recorded on a Sanborn Twinbeam Phonocardiograph at a paper speed of 75 cm. per second in 18 normal individuals, 25 patients with hypertensive vascular disease (diastolic pressure greater than 110 mm. Hg), and 10 patients with clinical and catheterization evidence of mitral stenosis. No patients with QRS intervals exceeding .10 second or with evidence of overt congestive heart failure or myocarditis were included. All patients studied had normal sinus rhythm and all of the hypertensive patients had either electrocardiographic or radiographic evidence of cardiac enlargement. The interval between the Q wave and the first heart sound, hereafter referred to as the Q-1 interval, was measured from the onset of electric systole to the first high-amplitude high-frequency vibrations of the first heart sound (fig. 1). The onset of electric systole was usually determined from the standard limb lead best delineating a Q wave. When a Q wave was not observed, the upstroke of the R wave in lead II was employed. Five sharply inscribed complexes were measured and the average was recorded to the nearest .005 second. All measurements were made from readings taken with the standard 50 mm. bell at the apex. With the paper speeds employed in this study, independent observations of the Q-1 interval agreed within .01 second. The data were analyzed statistically according to the methods outlined by Snedecor.[10]

## RESULTS

The results are summarized in table 1 and figure 2. The mean interval in the normal group was found to be .055 second (S. D. ± .01) with a range of .03 to .07 second. Only 1 subject in this group, an apparently healthy young adult, had a Q-1 time of .07 second. A

From the Department of Medicine, Duke University School of Medicine, and the Veterans Administration Hospital, Durham, N. C.

This research was supported in part by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract No. AF18(600) 1542, and by a research fellowship (Dr. Weissler) from the American Heart Association, and by a research grant (H-1217), and a Traineeship (Dr. Leonard) from the National Heart Institute, National Institutes of Health, U.S. Public Health Service.

TABLE 1.—*Mean Q-1, QRS, and R-R Intervals in Normal Subjects and Patients with Hypertension and Mitral Stenosis*

| | NO. | Q-1 | QRS | R-R |
|---|---|---|---|---|
| Normal | 18 | .055* (±.010) | .075 (±.007) | .81 (±.12) |
| Hypertension | 25 | .070 (±.009) | .090 (±.007) | .80 (±.14) |
| Mitral stenosis | 10 | .080 (±.010) | .080 (±.010) | .80 (±.11) |

*Seconds.

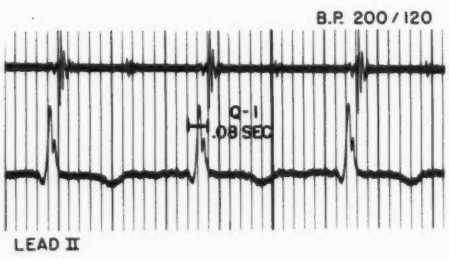


FIG. 1. The timing of the Q-1 interval from the beginning of the Q wave to the initial high-frequency vibrations of the first heart sound.

Q-1 interval of .07 second or greater was considered to represent abnormal delay in the appearance of the first heart sound.

The mean Q-1 interval for the patients with mitral stenosis was .08 second ( S. D. ± .01) with a range of .065 to .10 second. The mean Q-1 interval for the hypertensive group was .07 second (S. D. ± .009) with a range of .05 to .085 second, the values falling between the former groups. Of particular significance was the observation that 13 of the 25 hypertensive patients had Q-1 intervals of .07 second or greater.

The mean QRS and R-R intervals for the groups are also shown. The mean QRS interval for the hypertensive group was significantly greater than the normal subjects ($p < .01$). The length of this interval was poorly correlated with the QRS duration ($r = + .07$). No significant differences in the R-R intervals were observed.

In 3 of the hypertensive patients the administration of digitalis (Deslanoside, 1.6 mg. intravenously) failed to alter the Q-1 intervals.

## DISCUSSION

The measurement of the time interval between the onset of ventricular depolarization and the first heart sound has yielded somewhat different results in the hands of various investigators (table 2).[11] Such variability is due in part to differences in the timing of the onset of ventricular depolarization as judged from arbitrarily chosen standard limb leads, and to the variable inclusion of the initial low-frequency vibrations of the first heart sound in the measurement. In an attempt to control these factors better in the present study, the standard limb lead demonstrating the earliest onset of ventricular depolarization rather than any single arbitrarily chosen limb lead was employed for the timing of the Q wave, and the initial high-frequency high-amplitude vibrations of the first heart sound were selected for the timing of the first heart sound. When these criteria were used, the mean Q-1 interval in the normal group was .055 second (S. D. ± .010). Although the mean is slightly higher than that reported by most previous authors, the range of values is similar to those recently reported by Kelly[4] and Craige.[8] In the study of Braunwald, Fishman, and Cournand[12] on the time relationships of ventricular pressure curves in patients with a normal cardiovascular status, the mean interval from onset of the Q wave to the beginning of left ventricular systole was .052 second (S. D. ± .0067). This time corresponds well with the present data.

In an attempt to quantitate the delayed appearance of the first heart sound in mitral stenosis, it has been suggested that prolongation of the Q-1 interval to .07 second or greater, in the absence of bundle-branch block, be considered as strong evidence in favor of significant mitral stenosis.[4] In view of the present observations, however, we must modify our concept of the specificity of this finding, for it would appear that pathologic processes other than valvular stenosis can delay closure of the atrioventricular valves.

The present data do not elucidate the mechanism for the delayed appearance of the first heart sound in the hypertensive patient.

TABLE 2.—*Reported Observations on the Normal Q-1 Interval in Man**

| | Seconds |
|---|---|
| Weiss and Joachim | .05 —.07 |
| Gerhartz | .061 |
| Bull | .04 |
| Fahr | .02 —.03 |
| Lewis | .011—.039 |
| Battaerd | .02 —.065 |
| Kanner | .03 |
| Leblanc | .02 —.04 |
| Kelly | .04 |

*Adapted from Orias and Braun-Menéndez.[11]

Prolongation of the Q-1 interval might result from a slowing of either electric or mechanical events between the onset of depolarization and the appearance of the first heart sound. With respect to the former, prolongation of the depolarization process as evidenced by a significantly increased QRS interval was observed in the hypertensive group. However, only a poor correlation existed between the duration of depolarization and the Q-1 interval, indicating that other factors of a mechanical nature must also play a role. The lack of clinical evidence for congestive heart failure in the patients studied as well as the failure of digitalis to alter the Q-1 interval in 3 of the hypertensive subjects would tend to dismiss myocardial failure as an important factor. Another plausible explanation for the delayed first heart sound is a diminution in the rate of pressure rise during early ventricular systole. Although such a mechanism has been observed in patients with myocarditis,[4] there is presently no evidence of similar changes in patients with hypertension or ventricular hypertrophy.

The delayed appearance of the first heart sound in hypertensive patients helps in part to explain the frequent occurrence of an atrial gallop sound in these individuals.[13] Present evidence is consistent with the thesis that the gallop is produced by a separation of the early atrial components from the later major vibrations of the first heart sound.[9] The delayed appearance of the major vibrations of the first sound results in further separation of the 2 components, facilitating

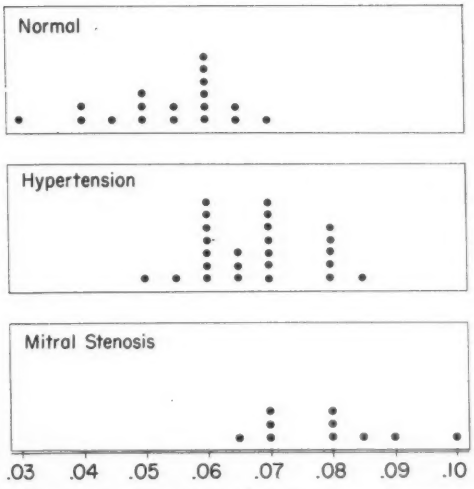


FIG. 2. Range of individual Q-1 interval measurements (seconds) in normal subjects and patients with hypertension and mitral stenosis.

their audibility as individual sounds. The atrial gallop phenomenon is frequently present in the absence of a prolonged Q-1 interval, suggesting that the mechanisms for these 2 phenomena are not interdependent.

In patients with rheumatic heart disease, the determination of the Q-1 interval alone or in combination with the measurement of the time between the second heart sound and the opening snap (2-OS time) offers a semiquantitative means of estimating the degree of mitral valvular stenosis.[3-8] Abnormal prolongation of the Q-1 interval, a very short 2-OS time, and a formula developed by Wells[3] relating the 2 measurements have been employed in various laboratories as criteria for significant, i.e., operable, mitral stenosis. As a consequence of the present observations and recent studies demonstrating that hypertension can increase the 2-OS time as well,[5] the phonocardiographer is confronted with considerable difficulty in evaluating patients with combined valvular disease and hypertension. It would appear that the presence of hypertension imparts the impression in the Q-1 interval, of a more severe stenosis, while in the 2-OS time, of a lesser degree of valvular stenosis than is actually present. It might be possible that employing the Well's formula

for assessment of the degree of stenosis, (Q-1 minus 2-OS), the deviations induced by hypertension would be mathematically cancelled. However, since the mechanism for prolongation of the Q-1 interval and that for increasing the 2-OS time are most probably different, it cannot be assumed that the effects of hypertension would be cancelled from a physiologic standpoint. In view of these observations one must exert considerable caution in the phonocardiographic evaluation of the patient with mitral stenosis and co-existent hypertension.


## Summary

The Q-1 interval is a measure of the time between onset of ventricular depolarization and the first heart sound. Prolongation of this interval has been noted frequently in patients with mitral stenosis.

Prolongation of the Q-1 interval was a frequent observation in 25 patients with severe hypertensive vascular disease, the range of values for this group falling midway between normal individuals and patients with mitral stenosis. While the mechanism for the delayed appearance of the first heart sound is not wholly elucidated, present evidence favors combined electric and mechanical factors. The importance of these observations in the phonocardiographic evaluation of patients with combined valvular disease and hypertension is stressed.

## Summario in Interlingua

Le intervallo Q-1 representa un mesura del tempore inter le initiation del dispolarisation ventricular e le prime sono cardiac. Prolongation de iste intervallo ha frequentemente essite notate in patientes con stenosis mitral.

Prolongation del intervallo Q-1 esseva un phenomeno frequente in 25 patientes con sever morbo vascular hypertensive. Le scala del valores in iste gruppo esseva intermediari inter illo in individuos normal e illo in patientes con stenosis mitral. Ben que le mechanismo responsabile pro le retardo del prime sono cardiac non es completemente elucidate, le datos nunc disponibile supporta le notion que il se tracta del effecto de un combination de factores electric e mechanic. Es signalate le importantia de iste observationes pro le evalutation phonocardiographic de patientes con morbo valvular e hypertension in combination.


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# Electrocardiographic Diagnosis of Ventricular Hypertrophy in the Presence of Right Bundle-Branch Block

*By* Richard W. Booth, M.D., Te-Chuan Chou, M.D., and Ralph C. Scott, M.D.

Forty-nine autopsied cases of complete and incomplete right bundle-branch block were studied with correlation of the electrocardiographic and anatomic diagnosis of ventricular hypertrophy. Twenty-six (53 per cent) of the cases showed anatomic evidence of right ventricular hypertrophy. The cases were studied for right ventricular hypertrophy according to the criteria of Barker and Valencia and of Milnor. Milnor's criteria resulted in frequent overdiagnosis while those that met Barker and Valencia's criteria usually but not invariably showed anatomic right ventricular hypertrophy. The electrocardiographic diagnosis of left ventricular hypertrophy was masked by the bundle-branch block in anatomically proved cases.

THE presence of right bundle-branch block appears to make the diagnosis of ventricular hypertrophy more difficult, but there have been few reports concerning this problem in the recent English literature. Those studies that have been made since the introduction of the 12-lead electrocardiogram have been mostly confined to correlations between the electrocardiogram and clinical findings.[1-3] Carouso and associates,[4] however, studied the pathology in 24 cases of right bundle-branch block and their conclusions conflicted with those arrived at on clinical grounds alone. A review of the literature reveals a considerable difference of opinion, not only as to the significance[5-7] and genesis[8] of right bundle-branch block, but also regarding its role in obscuring the diagnosis of left and right ventricular hypertrophy.[1-3] It has been contended by Barker[1, 2] that the diagnosis of left ventricular hypertrophy, though rendered more difficult, can often still be made. These concepts have also been upheld by Laham and associates.[3, 9]

The purpose of the present communication is to re-evaluate the accuracy of the diagnosis of ventricular hypertrophy in the presence of right bundle-branch block in a series correlating the electrocardiographic with the postmortem findings.

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## Methods and Material

All the Cincinnati General Hospital postmortem records* from the years 1950 to 1955 inclusive, comprising over 3,000 autopsies, were reviewed and those cases with an electrocardiographic diagnosis of right bundle-branch block were analyzed. The cases accepted were those in which a 12-lead electrocardiogram was available within 6 months of death, and where there was no pathologic evidence of myocardial infarction. Cases with infarction were excluded because of its possible effect upon the voltage of the QRS complexes.

The diagnosis of right bundle-branch block was made when the following criteria were present: (1) an S wave in lead I, (2) primary and secondary R waves in leads from the right precordium with the R′ exceeding the initial R wave in height, i.e., rsR′, rSR′, (3) delay in the onset of the intrinsicoid deflection in the right precordial leads greater than 0.05 second, (4) an S wave in $V_5$ or $V_6$, (5) no initial Q waves over the right precordium. The block was deemed incomplete if the QRS interval measured 0.08 to 0.11 second inclusive, and complete if the QRS interval measured 0.12 second or greater.†

The material was then analyzed as to the presence of associated right ventricular hypertrophy

*A few cases from Jewish Hospital, Cincinnati, Ohio, were also reviewed.

†The distinction between incomplete and complete right bundle-branch block listed above is based upon duration of the QRS and is the one used by Barker and Valencia.[2] If the criteria of onset of intrinsicoid deflection in $V_1$ are used, i.e., 0.05 to 0.075 for incomplete and 0.08 second or greater for complete right bundle-branch block, some shifting of records from incomplete to complete status and vice versa will occur. We believe, however, that this in no way changes the conclusions we have reached.

TABLE 1.—*Electrocardiographic and Postmortem Analysis, from Cases Showing Right Bundle-Branch Block*

| No. | Case & Age | Cardiac diseases | Heart Wgt./ Gm. | Pathology | | | | RVH | LVH | Electrocardiogram | | | | | | | RVH |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Thickness dilated | | | | | | RBBB | | QRS Dur. std. | V1 | | V2 | | |
| | | | | RV | LV | RV | LV | | | Comp. | Inc. | | O.I.D. | R′ | O.I.D. | R′ | |
| | | | | mm. | mm. | | | | | | | sec. | sec. | mm. | sec. | mm. | |
| 1 | E.J./40 | RHD-MS | 480 | 7 | 15 | Yes | No | Yes | Yes | . | x | 0.08 | 0.06 | 1 | 0.07 | 6 | No |
| 2 | M.S./73 | RHD-MI,MS,ASHD | 405 | 3 | 13 | No | No | No | Yes | x | . | 0.12 | 0.08 | 3.5 | 0.08 | 3.5 | No |
| 3 | J.J./70 | RHD-MS,AS,ASHD | 410 | 4 | 19 | No | No | No | Yes | . | x | 0.10 | 0.08 | 9 | 0.08 | 9 | No |
| 4 | F.S./65 | ASHD | 670 | 4 | 15 | Yes | Yes | Yes | Yes | x | . | 0.16 | 0.09 | 9 | 0.10 | 9 | No |
| 5 | T.B./69 | ASHD | 505 | 5 | 15 | No | No | Yes | Yes | x | . | 0.12 | 0.08 | 9 | 0.04 | No | No |
| 6 | W.M./85 | ASHD,CP,MPE | 475 | 5 | 14 | Yes | Yes | Yes | Yes | x | . | 0.12 | 0.09 | 8 | 0.08 | 20 | Yes |
| 7 | E.D./80 | HCVD,ASHD,AS | 585 | 4 | 17 | No | No | No | Yes | . | x | 0.11 | 0.09 | 11 | 0.06 | 5 | CVH |
| 8 | A.F./75 | ASHD,RHD-MVI | 345 | 3 | 15 | No | No | No | Yes | . | x | 0.10 | 0.07 | 13 | 0.07 | 11 | Yes |
| 9 | C.S./71 | HCVD,ASHD | 675 | 5 | 25 | No | No | Yes | Yes | . | x | 0.09 | 0.08 | 13 | 0.07 | 2 | Yes |
| 10 | I.S./81 | HCVD,ASHD | 410 | 3 | 12 | No | No | No | No | . | x | 0.08 | 0.07 | 4 | 0.06 | 10 | Yes |
| 11 | M.E./93 | ASHD | 295 | 4 | 12 | No | No | No | No | . | x | 0.10 | 0.06 | 5 | .. | No | No |
| 12 | E.P./72 | ASHD,RHD-AS,MI,MS | 595 | 3 | 15 | Yes | No | No | Yes | x | . | 0.12 | 0.13 | 6.5 | 0.09 | 11 & 17 in V3 | Yes |
| 13 | F.U./64 | ASHD | 380 | 4 | 18 | No | No | No | Yes | x | . | 0.16 | 0.09 | 11 | 0.08 | 6 | No |
| 14 | E.G./80 | HCVD-FPC | 420 | 3 | 16 | No | No | No | Yes | x | . | 0.16 | 0.09 | 8 | .. | No | No |
| 15 | W.B./73 | ASHD-FPC | 460 | 5 | 15 | Yes | Yes | Yes | Yes | x | . | 0.14 | 0.08 | 3.5 | .. | No | No |
| 16 | J.M./65 | ASHD | 390 | 4 | 16 | No | No | No | Yes | . | x | 0.10 | 0.09 | 6 | 0.09 | 2.5 | No |
| 17 | T.G./67 | HCVD,ASHD | 680 | 6 | 18 | Yes | Yes | Yes | Yes | x | . | 0.12 | 0.10 | 7 | 0.10 | 5 | No |
| 18 | E.P./79 | HCVD | 485 | 2 | 20 | No | No | No | Yes | x | . | 0.12 | 0.10 | 8 | 0.06 | 10 | No |
| 19 | F.D./61 | ASHD-PE | 525 | 4 | 12 | No | No | IWNM | IWNM | . | x | 0.10 | 0.10 | 3.5 | 0.06 | 2.5 | No |
| 20 | R.P./ | IASD | 590 | 10 | 15 | No | No | Yes | Yes | . | x | 0.10 | 0.09 | 11.5 | 0.05 | 18 | Yes |
| 21 | M.S./ | IASD | .. | 10 | 20 | No | No | Yes | Yes | . | x | 0.11 | 0.08 | 4.5 | .. | No | No |
| 22 | M.B./39 | IVSD | 410 | 12 | 13 | No | No | Yes | No | . | x | 0.10 | 0.08 | 11 | 0.09 | 14 | Yes |
| 23 | C.R./90 | ASHD,FAH | 340 | 4 | 16 | No | No | No | Yes | x | . | 0.12 | 0.08 | 9 | 0.08 | 1.5 | No |
| 24 | R.R./29 | RHD,AI,AS,MI,MS,TI | 490 | 12 | 17 | Yes | Yes | Yes | Yes | . | x | 0.08 | 0.06 | 1.5 | 0.08 | 1.5 | No |
| 25 | W.F./75 | ASHD | 310 | 7 | 12½ | Yes | Yes | Yes | No | x | . | 0.12 | 0.08 | 10 | 0.08 | 19 | Yes |
| 26 | E.D./ | ASHD,HCVD | 440 | 4 | 12 | No | No | IWNM | IWNM | . | x | 0.10 | 0.06 | 15 | 0.06 | 12 | Yes |
| 27 | R.W./15 | IVSD,PDA,COA | 500 | 6 | 10 | Yes | Yes | Yes | No | . | x | 0.09 | 0.05 | 2.5 | .. | No | LVH |
| 28 | J.K./79 | ASHD | 355 | 4 | 18 | No | No | No | Yes | x | . | 0.12 | 0.10 | 7 | 0.07 | 5 | No |
| 29 | A.J./62 | None | 320 | 2 | 12 | No | No | No | No | x | . | 0.12 | 0.07 | 2 | 0.09 | 4.5 | No |
| 30 | G.A./60 | CP | 545 | 11 | 12 | Yes | Yes | Yes | No | . | x | 0.10 | 0.07 | 10.7 | 0.07 | 14 | Yes |
| 31 | P.M./76 | None | 205 | Nor | Nor | No | No | No | No | x | . | 0.12 | 0.09 | 11 | 0.09 | 6 | No |
| 32 | W.M./75 | ASHD,HCVD | 355 | 6 | 16 | No | No | Yes | Yes | x | . | 0.12 | 0.08 | 4 | 0.08 | 3 | No |
| 33 | M.W./64 | None | 265 | 4 | 14 | No | No | No | No | x | . | 0.12 | 0.12 | 3 | 0.12 | 5 | No |
| 34 | G.W./54 | ASHD,HCVD,FF | 415 | 3 | 14 | Yes | Yes | No | Yes | x | . | 0.14 | 0.10 | 4.5 | .. | No | No |
| 35 | W.L./80 | ASHD,HCVD | 550 | 6 | 22 | Yes | Yes | Yes | Yes | . | x | 0.10 | 0.09 | 4 | .. | No | No |
| 36 | D.K./30 | PDA,ALCA | 850 | 21 | 17 | Yes | Yes | Yes | Yes | . | x | 0.08 | 0.05 | 27 | 0.04 | 8 | Yes |
| 37 | G.H./75 | ASHD,HCVD | 250 | 4 | 16 | No | No | No | Yes | . | x | 0.10 | 0.08 | 5 | 0.09 | 6.5 | No |
| 38 | W.C./70 | ASHD,HCVD | 760 | 9 | 24 | Yes | Yes | Yes | Yes | x | . | 0.12 | 0.11 | 11 | 0.07 | 7 | No |
| 39 | F.D./60 | RHD-MS | 350 | 7 | 15 | Yes | No | Yes | Yes | . | x | 0.07 | 0.05 | 1 | 0.05 | 7.5 | No |
| 40 | E.F./67 | ASHD | 410 | 4 | 18 | Yes | No | Yes | Yes | x | . | 0.12 | 0.08 | 4.5 | .. | No | No |
| 41 | L.M./25 | None | 315 | 2 | 12 | No | No | No | No | x | . | 0.16 | 0.12 | 5 | .. | No | No |
| 42 | F.W./75 | ASHD-HCVD | 530 | 4 | 17 | No | No | No | Yes | . | x | 0.10 | 0.09 | 3.5 | 0.09 | 2.5 | No |
| 43 | C.L./49 | RHD-MS | 570 | 3 | 14 | No | No | No | Yes | . | x | 0.08 | 0.06 | 2.5 | .. | No | No |
| 44 | V.M./54 | CP | 490 | 5 | 14 | No | No | Yes | Yes | . | x | 0.08 | 0.08 | 2.5 | 0.09 | 1 | No |
| 45 | F.M./75 | ASHD-CP | 505 | 7 | 18 | No | No | Yes | Yes | . | x | 0.10 | 0.08 | 4 | 0.08 | 5 | No |
| 46 | D.M./45 | CP | 600 | 6 | 14 | No | No | Yes | Yes | . | x | 0.10 | 0.08 | 6.5 | 0.07 | 9.5 | No |
| 47 | G.V.A./70 | ASHD | 430 | 4 | 18 | Yes | Yes | Yes | Yes | . | x | 0.10 | 0.05 | 3 | .. | No | No |
| 48 | E.R./36 | CP-Old and recent pulmonary emboli | 525 | 6 | 14 | No | No | Yes | Yes | . | x | 0.08 | 0.06 | 1.5 | 0.06 | 2.5 | No |
| 49 | L.B./45 | RHD-Mitral aortic & tricuspid involvement | 520 | 7 | 21 | No | No | Yes | Yes | . | x | 0.08 | 0.07 | 4 | 0.07 | 4 | No |

s defined by Barker and Valencia,[1, 2] i.e., right entricular hypertrophy is present if R′ in the precordial leads is greater than 10 mm. in height n incomplete right bundle-branch block, and 15 nm. in height in complete right bundle-branch lock.

Recently Milnor[17] listed additional criteria for he diagnosis of right ventricular hypertrophy. These criteria are (1) a QRS duration of less han 0.12 second, plus either (2) a mean frontal lane axis from +110° to ±180° or —91° to ±180° or (3) an R/S or R′/S ratio in $V_1$ greater han 1.0, providing the R or R′ wave in $V_1$ is greater than 0.5 millivolt. Our material has been valuated with the use of these criteria.

The diagnosis of left ventricular hypertrophy was made according to the combined criterias as listed by Scott and associates:[10] (1) left axis deviation with $R_1$ plus $S_3$ exceeding 25 mm.; S-T depressed greater than 0.5 mm. in the lead I or a T wave less than 1 mm. in lead I, (in the absence of digitalis) (2) a negative deflection in $aV_R$ greater than 14 mm., (3) an R wave in lead $aV_L$ greater than 11 mm. in a horizontal heart, (4) an R wave $aV_F$ greater than 20 mm. in a vertical heart, (5) an R wave in $V_5$ or $V_6$ greater than 26 mm., (6) R in $V_5$ or $V_6$ plus the S in $V_1$ exceeding 35 mm., (7) QRS duration increased to 0.10 or 0.11 second; T-wave inversion in $V_5$ or $V_6$ with S-T depression (in the absence of digitalis); (8) delay in the onset of the intrinsicoid deflection between 0.05 and 0.07 in $V_5$ or $V_6$. If one or more of the criteria were met, left ventricular hypertrophy was considered to be present. This method of diagnosis has been found to be accurate in 96 per cent of the cases (in the absence of right bundle-branch block) in patients with proved left ventricular hypertrophy.[10] Combined ventricular hypertrophy was considered to be present only if the criteria for both left and right hypertrophy as listed above were met.

The electrocardiograms were divided into 2 main groups, incomplete and complete right bundle-branch block, according to the criteria previously given. The onset of the intrinsicoid deflections in leads $V_1$ and $V_2$ and the height and duration of the R′ in $V_1$ and $V_2$ were measured, as were the depth of the S in $V_{1, 2, 5, 6}$ and the height of the R in $V_5$ and $V_6$. The presence or absence of Q waves in the left precordial leads was noted and all tracings were analyzed for a possible diagnosis of left and right ventricular hypertrophy, according to the criteria previously mentioned.

The pathologic criteria for right ventricular hypertrophy were that the heart weight exceeded the normal as determined by Zeek[11] and the right ventricle was 5 mm. or greater in thickness if not dilated, or 4 mm. if a definite statement of dilatation was found in the protocol.[12] Left ventricular hypertrophy was considered to be present if the heart weight was increased[11] and the left ventricle measured 14 mm. or greater or 13 mm. if a definite statement of dilatation was found in the protocol. The ventricular measurements were made by different prosectors over a period of years, but the technic was reasonably constant and is listed as the greatest thickness from epicardium to endocardium.

TABLE 2.—*An Analysis of the Anatomic Findings with Regard to Ventricular Hypertrophy in 49 Cases of Right Bundle-Branch Block*

| Autopsy findings | Number of cases | Per cent of total |
|---|---|---|
| Isolated right ventricular hypertrophy | 4 | 8.0 |
| Isolated left ventricular hypertrophy | 15 | 30.5 |
| Combined ventricular hypertrophy | 22 | 45.0 |
| No ventricular hypertrophy | 6 | 12.5 |
| Increased weight but normal ventricular measurements | 2 | 4.0 |
| Total | 49 | 100.0 |

## RESULTS

As indicated in table 1 cases were analyzed for age, pathologic cardiovascular diagnosis, body size,* heart weight, left and right ventricular thickness at postmortem examination, and in addition whether or not ventricular dilatation was present.

In this series of 49 cases, unselected as to anatomic diagnosis (table 2), there were only 6 (12 per cent) normal hearts. Four (8 per cent) had isolated right ventricular hypertrophy, 15 (30 per cent) had isolated left ventricular hypertrophy and 22 (45 per cent) showed combined left and right ventricular hypertrophy. In addition, there were 2 hearts with increased weights but normal measurements of the ventricular walls.

*Not listed because of space limitation.

*Footnote for Table 1*

RHD, rheumatic heart disease; MS, mitral stenosis; MI, mitral insufficiency; ASHD, arteriosclerotic heart disease; HCVD, hypertensive cardiovascular disease; AS, aortic stenosis, IASD, interatrial septal defect; IVSD, interventricular septal defect, PDA, patent ductus arteriosus; IWNM, increased weight with normal wall measurements; MVI, mitral valve involvement; O.I.D., onset of intrinsicoid deflection; CP, cor pulmonale; ALCA, anomalous left coronary artery; FF, focal fibrosis; COA, coarctation of aorta; FAH, focal amyloidosis of the heart; PE, pulmonary embolus; EPC, fibrinous pericarditis; MPE, multiple pulmonary emboli.

TABLE 3.—*A Correlation of the Electrocardiographic Diagnosis with the Postmortem Findings in 49 Cases of Right Bundle-Branch Block*

| Electrocardiographic Diagnosis | Total | Diagnosis | Cases | Postmortem findings: RVH | LVH | CVH | No Hy. | IWNM |
|---|---|---|---|---|---|---|---|---|
| Incomplete right bundle-branch block | 28 | RVH | 8 | 2 | 1 | 3 | 1 | 1 |
| | | LVH | 1 | 1 | 0 | 0 | 0 | 0 |
| | | CVH | 1 | 0 | 1 | 0 | 0 | 0 |
| | | No Hy. | 18 | 0 | 5 | 11 | 1 | 1 |
| Complete right bundle-branch block | 21 | RVH | 3 | 1 | 1 | 1 | 0 | 0 |
| | | LVH | 0 | 0 | 0 | 0 | 0 | 0 |
| | | CVH | 0 | 0 | 0 | 0 | 0 | 0 |
| | | No Hy. | 18 | 0 | 7 | 7 | 4 | 0 |
| Total | 49 | | 49 | 4 | 15 | 22 | 6 | 2 |

RVH, right ventricular hypertrophy; LVH, left ventricular hypertrophy; CVH, combined ventricular hypertrophy; No Hy., no ventricular hypertrophy; IWNM, increased heart weight with normal ventricular measurements.

*Incomplete Right Bundle-Branch Block.* As noted in table 3, 28 cases met the criteria for incomplete right bundle-branch block. There were 8 cases that fulfilled Barker and Valencia's criteria for co-existing right ventricular hypertrophy, i.e., right precordial R′ greater than 10 mm. At autopsy, of these 8 cases 2 had right ventricular hypertrophy, 1 had left ventricular hypertrophy, 3 had combined ventricular hypertrophy, 1 had no hypertrophy, and there was 1 with increased weight but normal measurements.

In addition to the 8 cases mentioned above, there was 1 case that also met the electrocardiographic criteria for left ventricular hypertrophy, but had right ventricular hypertrophy at postmortem examination and 1 that showed combined ventricular hypertrophy on the electrocardiogram but only left ventricular hypertrophy postmortem. At autopsy the remaining 18 cases with no electrocardiographic evidence of ventricular hypertrophy showed left ventricular hypertrophy in 5, combined ventricular hypertrophy in 11, no hypertrophy in 1, and there was 1 case with increased weight but normal wall measurements. Of the 5 cases of congenital heart disease all had incomplete block and 3 showed associated right ventricular hypertrophy on electrocardiogram. All had anatomic right ventricular hypertrophy.

Twenty-six of our cases of incomplete right bundle-branch block were also analyzed according to Milnor's criteria.[17] Three of these had isolated right ventricular hypertrophy; 7 isolated left ventricular hypertrophy; 12 combined ventricular hypertrophy, 1 no ventricular hypertrophy, and 3 with increased weight and normal ventricular wall measurement at postmortem examination. Fifteen of the 26 met Milnor's criteria for right ventricular hypertrophy on the electrocardiogram. The diagnosis was correct in 9 (60 per cent) and erroneous in 6 (40 per cent). In addition 7 cases with combined ventricular hypertrophy were missed as was 1 case of isolated right ventricular hypertrophy, although this was admittedly a borderline one with a frontal plane axis of +102°.

*Complete Right Bundle-Branch Block.* The 21 cases of complete right bundle-branch block (table 3) revealed 3 with electrocardiographic evidence of associated ventricular hypertrophy, i.e., R′ greater than 15 mm. over the right precordium. At autopsy 1 had right ventricular hypertrophy, 1 left ventricular hypertrophy, and 1 combined ventricular hypertrophy. The remaining 18 cases that showed no electrocardiographic evidence of ventricular hypertrophy showed left ventricular hypertrophy in 7, combined ventricular hypertrophy in 7, and no ventricular hypertrophy in 4.

*Comment.* Left ventricular hypertrophy, although present anatomically as an isolated finding in 15 cases, could be interpreted on the electrocardiogram in only 1 case. The bundle-branch block was equally effective in masking an enlarged left ventricle whether it was complete or incomplete.

A total of 11 cases met the criteria of Barker and Valencia for associated right ventricular hypertrophy. It would appear that the right ventricle was indeed enlarged in 7 of these cases for a total of 64 per cent, although

in 4 of these left ventricular hypertrophy was also present.

## Discussion

An analysis of our data leads to the conclusion that in cases unselected as to postmortem etiologic diagnosis, the presence of right bundle-branch block, either complete or incomplete, does not necessarily indicate right heart hypertrophy or even heart disease at all. In 28 cases of incomplete right bundle-branch block there were 2 with normal hearts and in 21 with complete right bundle-branch block there were 4 with normal hearts. In fact, isolated left ventricular hypertrophy was far more common than isolated right ventricular hypertrophy in our series. These findings are at some variance with those of Mounsey and co-workers[7] who analyzed clinically 16 cases of emphysema and thought that an RSR′ was usually, but not invariably, associated with right ventricular hypertrophy. Friedland and associates[15] found right ventricular hypertrophy in 70 per cent of cases with incomplete right bundle-branch block and it has been stated by Levine[16] that persistent incomplete right bundle-branch block is presumptive evidence of right ventricular hypertrophy.

Carouso and associates[4] also have indicated that they consider an rR′ or rsR′ suggestive of right ventricular hypertrophy. Their conclusions were reached after postmortem studies, but their series was limited to cases with proved right ventricular hypertrophy. This perhaps may account for different results.

Laham and associates[3, 9] analyzed on clinical grounds 62 cases of right bundle-branch block, about half complete and half incomplete. They found 38 (61 per cent) with right ventricular hypertrophy, 21 (34 per cent) with left ventricular hypertrophy and 3 (5 per cent) with combined ventricular hypertrophy. Our pathologic correlation revealed right ventricular hypertrophy as an isolated lesion in only 4 cases (8 per cent), left ventricular hypertrophy in 15 (30 per cent), about the same as Laham, but combined ventricular hypertrophy was present in 22 (45 per cent), a much higher figure. This probably reflects the difficulty in making the clinical diagnosis of combined ventricular hypertrophy. In all, a total of 26 of our 49 cases (53 per cent) had an enlarged right ventricle either isolated or combined with enlargement of the left.

After analyzing our cases we agree, therefore, with Myers and associates[6] who think that right bundle-branch block is merely suggestive, but certainly not pathognomonic, of right ventricular hypertrophy. In unselected cases right bundle-branch block is asociated with enlargement of the left ventricle, either alone or in combination with right ventricular hypertrophy in too many cases to render it a significant sign of an isolated right ventricular lesion.

On the other hand the views of Said and Bryant[5] and Camerini and Davies[13] that incomplete right bundle-branch block is often found in normal subjects in no way detracts from its significance and the ability of this disturbance to obscure the electrocardiographic evidence of left ventricular hypertrophy remains a fact. An attempt was made to correlate the electrocardiographic diagnosis of right, left, or no ventricular preponderance with the ratio of right ventricular to left ventricular thickness in millimeters. Such an analysis failed to reveal the expected relationship that increasing mass of one ventricle would produce a more frequent electrocardiographic diagnosis of preponderance of said chamber.

In addition, if one attempts to relate the height of the R′ wave over the right precordium to the ratio right ventricle/left ventricle thickness in millimeters, there can be noted no correlation between the voltage produced over the right precordium and the relative preponderance of the left or right ventricle.

Torner-Soler and associates[8] considered that the blood pressure in the right ventricle correlates with the height of the R in right ventricular hypertrophy or the R′ in incomplete right bundle-branch block especially in congenital heart disease. On the other hand, Scott and associates[14] found that in their series of 28 cases of chronic cor pulmonale that had been catheterized, that incomplete

right bundle-branch block might occur at all levels of mean pulmonary artery pressure.

In essence, the genesis of the voltage of the R′ wave remains obscure with neither ventricular mass nor mean pressure always producing a predictable effect.

*The Diagnosis of Right Ventricular Hypertrophy.* The diagnosis of right ventricular hypertrophy co-existing with right bundle-branch block, complete or incomplete, is not obscured in the opinion of Barker.[1, 2] On clinical grounds he thought that in nearly every instance of this combined hypertrophy-block pattern, as Torner-Soler terms it, right ventricular hypertrophy can be demonstrated.

Laham and associates[3, 9] also considered that a tall R′ over the right precordium, which was present in 24 of 38 cases, believed to have on radiologic and clinical grounds right ventricular hypertrophy, was a valuable diagnostic sign. They added that this was true especially in cases that had a condition capable of overloading the right ventricle. They also thought that over the age of 40 the R′ can be over 10 mm. without right ventricular hypertrophy. Although our postmortem cases range in age mostly above 40 we would certainly agree that the criteria for right ventricular hypertrophy in the electrocardiogram can be met and right ventricular hypertrophy not be found on postmortem examination in older patients who do not have a condition producing right ventricular over-loading.

In the study of Torner-Soler et al.[8] 3 cases met the criteria for right ventricular hypertrophy and right bundle-branch block. All 3 had marked right ventricular hypertension when catheterized. In an over-all analysis of their cases it was noted, however, that the height of the R wave corresponded to the degree of right ventricular hypertension much better in congenital than in acquired heart disease.

Of our 11 cases that met the criteria for associated right ventricular hypertrophy, 7 (64 per cent) had right ventricular hypertrophy at postmortem examination. It is interesting to note that Carouso and associates[4] in 24 cases of right ventricular hypertrophy confirmed post mortem found only 3 cases with an R′ in the electrocardiogram greater than 10 mm. Although we had only 4 cases of isolated right ventricular hypertrophy, 3 of these 4 did have tall R′ waves over the right precordium. These criteria obviously consistently miss the diagnosis of right ventricular hypertrophy when it is combined with left ventricular hypertrophy.

Utilizing the criteria of Milnor[17] for the diagnosis of right ventricular hypertrophy, we found that this method will frequently make the diagnosis of right ventricular hypertrophy when it is not present anatomically, 6 cases (40 per cent) in our series. These criteria cannot be fairly judged for accuracy with regard to isolated right ventricular hypertrophy, as only 3 cases were in this group. When both ventricles were hypertrophied, however, the diagnosis could be made electrocardiographically in only 5 of 12 cases (42 per cent). It would appear, therefore, that in our series the usefulness of these criteria is limited by the fact that overdiagnosis of right ventricular hypertrophy may result.

*Diagnosis of Left Ventricular Hypertrophy.* Barker[1] has indicated that he considers the diagnosis of left ventricular hypertrophy is difficult, although it can still be made, in the presence of right bundle-branch block. Laham and associates[3, 9] believed that they could make the diagnosis of associated left ventricular hypertrophy in 60 per cent of their cases on clinical grounds.

In our series this diagnosis was made only once by means of all available criteria. The one case that fulfilled the criteria at postmortem studies revealed isolated right ventricular hypertrophy. In our series, besides the 15 cases of isolated left ventricular hypertrophy there were 22 additional cases of combined ventricular hypertrophy or a total of 37 cases that had an enlarged left ventricle. The electrocardiographic diagnosis was obscured in all.

## Summary and Conclusions

Electrocardiograms from 49 cases of right bundle-branch block that have come to autopsy have been reviewed and analyzed. The re

sults are discussed in terms of both the pathologic and electrocardiographic diagnosis of right and left ventricular hypertrophy.

The results indicate that in our series (1) of 49 cases of right bundle-branch block, unselected as to pathologic diagnosis, only 26 (53 per cent) showed anatomic evidence of right ventricular hypertrophy. (2) Those cases with electrocardiograms that met Barker and Valencia's criteria for co-existing right ventricular hypertrophy frequently, but not invariably, displayed right ventricular hypertrophy post mortem, the percentage being higher in congenital than in acquired heart disease. (3) Anatomic left ventricular hypertrophy, either isolated or combined, was consistently masked in the electrocardiogram by both complete and incomplete right bundle-branch block, (4) Utilization of the criteria proposed by Milnor for the diagnosis of associated right ventricular hypertrophy resulted in frequent overdiagnosis. The genesis of a tall R′ in right bundle-branch block over the right precordium is discussed and it is concluded that at this time neither the muscle mass nor the mean pressure in the right ventricle or pulmonary artery can be consistently correlated with it.


### Summario in Interlingua

Es passate in revista e analysate le electrocardiogrammas ab 49 casos de bloco de branca dextere pro le quales reportos necroptic esseva disponibile. Le resultatos es discutite con referentia al diagnose tanta pathologic como etiam electrocardiographic de hypertrophia dextero- e sinistro-ventricular.

Le sequente observationes resulta del datos in nostre serie. (1) Inter 49 casos de bloco de branca dextere, solmente 26 (i.e. 53 pro cento) exhibiva signos anatomic de hypertrophia dextero-ventricular. (2) Le casos con electrocardiogrammas que satisfaceva le criterios de Barker e Valencia pro le co-existentia de hypertrophia dextero-ventricular exhibiva frequente—sed non invariabilemente hypertrophia dextero-ventricular al necropsia. Le procentage esseva plus alte in morbo cardiac congenite que in morbo cardiac acquirite. (3) Hypertrophia sinistro-ventricular, isolate o combinate, ben que anatomicamente evidente, esseva uniformemente mascate in le electrocardiogramma per complete e incomplete bloco de branca dextere. (4) Le uso del criterios proponite per Milnor pro le diagnose de associate hypertrophia dextero-ventricular resultava frequentemente in diagnoses falsemente positive. Le genese de un alte R′ in bloco de branca dextere supra le precordio dextere es discutite. Es concludite que al tempore presente ni massa muscular ni le pression medie in le ventriculo dextere o in le arteria pulmonar pote esser correlationate con illo de maniera uniforme.


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**Caniggia, A., and Bertelli, G.: The Esophageal Electrocardiogram in Paroxysmal Tachycardia and in Auricular Flutter before and after Treatment by Quinidine and Procaine Amide.** Acta cardiol. **12**: 356 (Fasc. 4), 1957.

The usefulness of esophageal leads in detection of atrial activity and in the differentiation of mechanisms of arrhythmias is illustrated by examples of a wandering pacemaker and of an atrial tachycardia with bundle-branch block simulating ventricular tachycardia. The recording of atrial and ventricular proximity potentials with the help of esophageal leads permits the demonstration of a different pharmacologic mechanism; by which quinidine and procaine amide suppress various types of ectopic impulse formation. Widening of P waves and QRS complexes following quinidine suggests that its action is mainly one of slowing of impulse transmission. Procaine amide on the other hand, does not affect the contour of the esophageal P waves, and hence appears to influence primarily the excitability of abnormal centers.

Pick

# Effect of Cooling and of Smoking Tobacco upon the Blood Flow of Reactive Hyperemia of the Foot

*By* JAY D. COFFMAN, M.D., J. EDWIN WOOD, M.D., AND ROBERT W. WILKINS, M.D.

Tobacco smoking and body cooling have been shown to decrease the "resting" blood flow to the foot. The present study was designed to determine whether either of these 2 stimuli also affects the increased blood flow that follows a period of ischemia (reactive hyperemia). Blood flows to the foot were measured in subjects with and without vascular disease by the venous occlusion, water plethysmographic method in a warm and a cool environment before and during smoking. Patients with bilaterally and unilaterally sympathectomized limbs were also studied to determine the mechanism of the observed responses.

THE peripheral vasoconstrictor effects of tobacco smoking or body cooling are well known and have been demonstrated by several observers.[1-3] Recently, it has been shown in this laboratory that the smoking of 2 cigarettes produces a definite decrease of resting blood flow in the foot of approximately 90 per cent of subjects studied plethysmographically.[4] This decrease in resting blood flow caused by smoking was less than that produced by a cool environment. The present investigation was designed to measure the effect of tobacco smoking and body cooling on the peripheral circulation during one condition of increased need namely the increase of blood flow following a period of ischemia of a limb, commonly referred to as *reactive hyperemia blood flow.*

## METHOD

Measurements of foot blood flow were obtained by the venous occlusion plethysmographic method on patients with and without vascular disease. The subjects, who varied in age from 16 to 72 years, were habitual smokers. Studies were performed in a constant temperature room with the lightly clothed subject in the supine position. The subject's slightly elevated foot and ankle were enclosed in the Wahmann Foot plethysmograph* filled with water at a temperature of 89 F., in both the warm (83 F.) and the cool (68 F.) environment. This position brought the posterior aspect of the lower leg and foot approximately to heart level. The technic used for enclosing the foot in the water plethysmograph has been previously described in detail.[4, 5] The water level within the plethysmograph produced a hydrostatic pressure equal to or slightly greater than natural local venous pressure.[5] Inflation of a 13-cm. wide blood pressure cuff applied at the ankle just proximal to the plethysmograph produced the venous occlusion necessary to measure blood flow. Arterial occlusion was produced by inflating a similar cuff applied 3 cm. below the knee. The rate of change of foot volume was recorded by means of a volume calibrated Brodie bellows. The lowest venous occlusion pressure required to obtain the maximum rate of increase in foot volume was determined at the beginning of each experiment and averaged 41 mm. Hg. This pressure was then used throughout the experiment. Arterial occlusion pressure was set at 50 mm. Hg above the patient's systolic blood pressure as measured in the arm by the auscultatory method. Leakage of blood from the arteries into the foot beneath the cuff could be detected by a rise in volume of the foot during the occlusion period. The volume of foot within the plethysmograph was determined after the experiment by displacement. A thermocouple was applied to the tip of the opposite great toe for measuring skin temperature.

The general protocol of each experiment is illustrated in figure 1. The patients were acclimated to room temperature (warm and cool) for at least 1 hour and for whatever additional time was required to obtain relatively constant blood flow and skin temperature measurements. Then 3 resting blood flows were obtained every 5 minutes for 15 minutes. The mean resting blood flow for this period is plotted in figure 1. Arterial occlusion of 5 minutes' duration, indicated by zero flow, was then applied. Following release of arterial occlusion, blood flow measurements were repeated at 15-second intervals for 2 minutes and then at 30-second intervals for a further 6 minutes. Another

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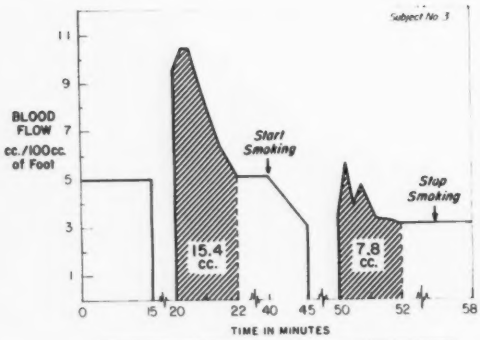
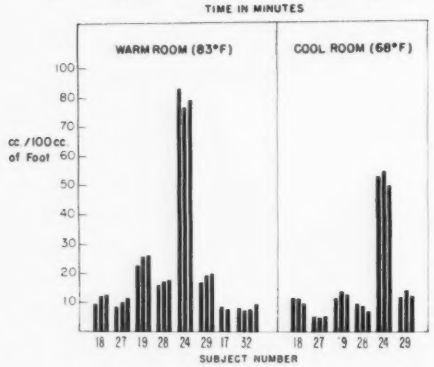


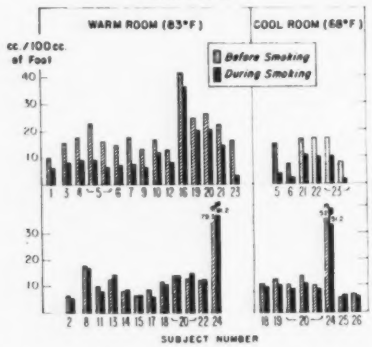




FIG. 1 *Top.* The experimental protocol and method of calculating reactive hyperemia blood flow.

FIG. 2 *Middle.* The variability of reactive hyperemia blood flow with repeated determinations on the same subject without smoking, in a constant temperature environment.

FIG. 3 *Bottom.* The effect of smoking upon reactive hyperemia blood flow in warm and cool environments. The upper panel is composed of those subjects considered to have had significant decreases in reactive hyperemia blood flow; the lower panel, those subjects with insignificant changes.

series of resting blood flows was obtained as described above.

The subject then smoked 2 regular type cigarettes at his own rate, requiring about 14 minutes. (No king size, low nicotine, or filtered cigarettes were used.) Five minutes after smoking began, arterial occlusion was reapplied and the previous observations were repeated. Blood flow to the foot was expressed in milliliters per minute per 100 ml. of foot tissue.

It was necessary to select a single time period for the reactive hyperemia phase in comparing data from different experiments. Vasodilatation usually persisted for at least 2 minutes; almost invariably the total duration of control reactive hyperemia was the same as or longer than its paired smoking reactive hyperemia (in 50 of 55 pairs). Therefore, the 2-minute period was selected and is indicated by the dotted lines in figure 1. By means of a planimeter, it was then possible to measure the total area within each curve and convert this mathematically to ml. per 100 ml. of foot tissue. The value obtained was the volume of blood that had passed through 100 ml. of foot tissue during the 2-minute period that followed release of the arterial occlusion. It will be referred to hereafter as RHBF (reactive hyperemia blood flow). In subject number 3 (fig. 1) this value was 15.4 ml. before smoking and 7.8 ml. during smoking.

The spontaneous variation of RHBF without smoking was investigated by measuring RHBF repeatedly under the standard experimental conditions described above.

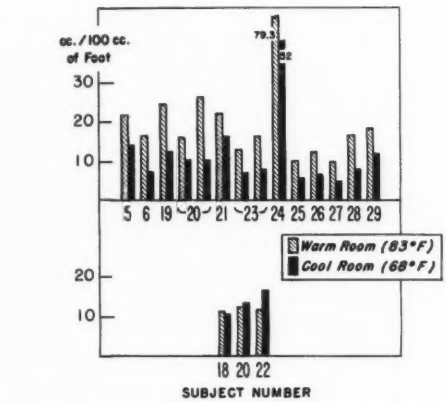
## RESULTS

### I. *Variation of RHBF*

As shown in figure 2, 3 RHBFs in the warm, and 3 in the cool environment were determined on 6 subjects; data were obtained on 2 more subjects in the warm room only. The greatest variation among subjects who showed a RHBF less than 26 ml. per 100 ml. of foot tissue was 3.5 ml. Therefore only changes in RHBF greater than this value were considered to be of importance. One other subject had cirrhosis of the liver (patient 24) associated with an exceptionally high RHBF. The variation of RHBF was greater in this subject than that of the above group (6.7 ml.).

### II. *Warm Room Experiments*

Figure 3 shows the RHBFs before smoking and during smoking in the room at 83 F. in 27



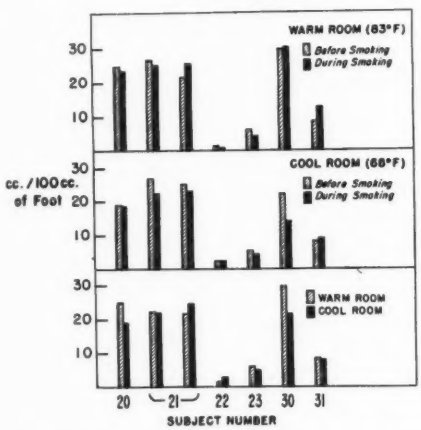




FIG. 4 *Top.* The effect of cooling the environment upon reactive hyperemia blood flow. The upper panel is composed of those subjects considered to have had significant decrease in reactive hyperemia blood flow; the lower panel, those subjects without significant change.

FIG. 5 *Bottom.* The effect of smoking in the warm environment (*upper panel*), smoking in the cool environment (*middle panel*) and of the cool environment, compared with the warm environment (*lower panel*) upon reactive hyperemia blood flow of sympathectomized limbs.

experiments. The upper half of the figure shows 15 studies in which smoking reduced the RHBF. Two experiments on separate days were performed on subject number 5 and showed comparable responses. Subject number 20 showed no response to smoking in his right foot until after his *left* limb had been sympathectomized. The lower half of the figure shows 12 subjects in whom the RHBF remained the same, increased, or decreased by less than the variation described above. The 27 control RHBFs averaged 18.0 ml. per 100 ml. of foot tissue (6.3 to 79.3 ml.). The 27 RHBFs during smoking averaged 13.7 ml. per 100 ml. of foot tissue (3 to 81.2 ml.).

III. *Cool Room Experiments*

Figure 3 also shows the RHBFs before smoking and during smoking in the room at 68 F. in 14 experiments. Smoking produced a definite decrease in RHBF in 6 of the 14 studies. Repeat experiments performed on different days show comparable responses in both subjects (number 23 and number 20). In the cool room experiments 14 control RHBFs averaged 13.6 ml. (5.5 to 52.0 ml.), while 14 RHBFs during smoking averaged 9.9 ml. per 100 ml. of foot tissue (1.3 to 51.2 ml.).

IV. *Comparison of Control Warm and Cool Room RHBFs*

Figure 4 demonstrates the decrease in RHBF produced by cooling the environment. Of the 17 experiments, 14 showed a definite reduction of RHBF by cooling from 83 to 68 F. Subject number 23 showed comparable responses on 2 different days. Following cooling, subject number 20 had a greater decrease in RHBF in his right foot after his *left* leg had been sympathectomized. The 17 RHBFs in the warm room averaged 19.9 ml. (9.9 to 79.3 ml.) while the 17 RHBFs in the cool room averaged 12.6 ml. per 100 ml. of foot tissue (4.7 to 52.0 ml.).

V. *Experiments on Sympathectomized Patients*

Seven sympathectomized legs of 6 patients were studied in both the warm and cool environment as shown in figure 5. In the room at 83 F. smoking produced no change in the RHBF. The control RHBFs averaged 17.0 ml. while the RHBFs during smoking averaged 17.5 ml. Two of the 7 studies in the 68 F. room showed a decrease of RHBF during smoking (subjects 21 and 30). The 7 control

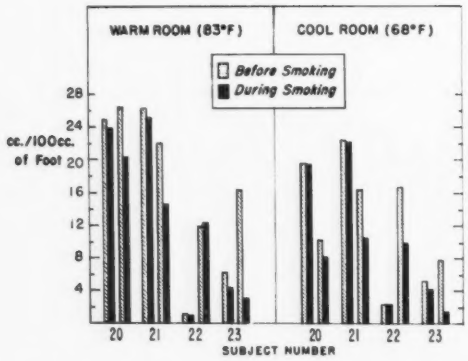



FIG. 6. The effect of smoking upon the reactive hyperemia blood flow of a sympathectomized and an unsympathectomized foot studied simultaneously. The first pair of bars represent the results of study of the sympathectomized foot in each case.

RHBFs in the cool room averaged 15.4 ml. while the 7 RHBFs during smoking averaged 13.3 ml. Cooling from 83 to 68 F. produced no reduction in RHBF in 5 of the 7 sympathectomized limbs; the RHBFs averaged 16.4 and 14.7 ml. in the warm room and in the cool room, respectively. (The small blood flows of subject number 22 presumably were due to thromboangiitis obliterans.)

Four of these patients had unilateral lumbar sympathectomies and were studied with simultaneous blood flow measurements of both feet by means of 2 plethysmographs. Except for the additional plethysmograph the same procedure as described above was used. The sympathectomized feet showed no change in RHBF during smoking in the 8 warm and cool room studies; the unsympathectomized feet showed a definite reduction of RHBF during smoking in 6 of the 8 experiments (fig. 6).

Fourteen of the 27 subjects were considered to have peripheral vascular disease that was vasospastic in origin. There was no apparent accentuation of the response to smoking or to cooling in these 14 patients. There were 10 subjects with normal circulation, 3 subjects with mild arteriosclerosis obliterans, 1 subject with severe arteriosclerosis obliterans, and 1 subject with thromboangiitis obliterans. Two patients (subjects number 16 and 24) had increased peripheral circulation associated with cirrhosis of the liver and 1 patient had terminal vessel occlusions in the toes due to a secondary polycythemia.

## DISCUSSION

Total reactive hyperemia blood flow presumably includes the blood flow through arteriovenous shunts as well as blood flow through nutrient capillaries of the foot. A portion of the capillary blood flow supplies resting metabolic needs of the tissue, a portion meets the unsupplied metabolic needs of the previously ischemic tissue, and a portion may be metabolically superfluous. Despite the possibility of such varied metabolic and nonmetabolic routes of reactive hyperemia blood flow, a reduction of this total flow by reflex vasoconstrictor stimuli would suggest that those stimuli prevented the tissue metabolic requirements from being satisfied as efficiently as before. While this result might be of little consequence to an individual with a normal circulation, it conceivably would be important to a patient with advanced peripheral vascular disease. The action of such reflex vasoconstrictor stimuli on reactive hyperemia blood flow has not been investigated previously but it has been mentioned briefly in connection with peak blood flows in the toe.[6, 7] In the present study the vasoconstrictor effects of tobacco smoking and of reflex body cooling on reactive hyperemia of the foot (which is predisposed to the complications of occlusive vascular disease) have been investigated.

It has been shown by other workers that smoking produces a decrease in skin temperature.[8] Since changes in local temperature affect reactive hyperemia,[9, 10] probably as a result of altered local metabolic requirement the water in the foot plethysmograph was maintained at a constant 89 F. In this manner, the effects of smoking or of a cool body environment were not influenced by change in water temperature surrounding the foot.

Reactive hyperemia is often reported in terms of the blood flow in excess of mean rest

ing blood flow. However the blood flow in the foot is quite variable, particularly during smoking, as has been previously shown.[4] For this reason, it would be difficult to predict the mean resting blood flow that would have been present had no arterial occlusion been performed. Therefore, the total postischemia blood flow was considered to be a more objective measurement. In so far as possible, the data were also calculated to determine the blood flow in excess of presumed resting blood flow. Mean blood flow immediately following the reactive hyperemia phase was used as the resting blood flow. The effects of smoking and body cooling upon reactive hyperemia were qualitatively the same, regardless of the method of calculation, with few exceptions.

In the studies of the variation of the measurement of RHBF, the first determination in 5 experiments in the warm room was less than the second or third RHBFs. Eichna and Wilkins[11] and Patterson and Whelan[12] have pointed out that the *peak* or maximal blood flow obtained during reactive hyperemia is lower in the first than in the subsequent 2 or 3 of a series but then becomes remarkably constant in the forearm. The latter authors did not find that this phenomenon of "augmentation of successive flows" applied to the total reactive hyperemia blood flow calculated as the excess over resting blood flow, but the present figures differ from those in that the present ones give the total postischemia blood flow to the foot. There was no consistent tendency for the foot RHBF so calculated to *decrease* in either the warm or the cool environment during the course of the present experiments.

In 15 of 27 warm (83 F.) room, and in 6 of 14 cool (68 F.) room experiments, the smoking of 2 cigarettes decreased the RHBF to the foot. These patients also showed a decrease in skin temperature as measured in the contralateral foot, averaging 5.7 F. and ranging from 1.5 to 11 F.

In 14 of 17 experiments, it was demonstrated that cooling the environment from 83 to 68 F. definitely decreased RHBF of the foot although the water temperature in the plethysmograph was maintained constant at 89 F. These studies show that smoking may reduce the total amount of blood flow to a previously ischemic foot in certain individuals, but that body cooling is the more consistent stimulus in this regard. The decrease of RHBF of the foot by body cooling does not necessarily prevent a further reduction by smoking, as was demonstrated by 5 of our subjects. This would suggest that these 2 stimuli may be at least additive.

In many of the subjects in these studies, smoking or cooling also produced a lower level of resting blood flow. However, there was no apparent correlation between the degree of reduction of RHBF and the degree of reduction of resting blood flow during these vasoconstrictor stimuli.

The experiments performed on patients with lumbar sympathectomies indicate that smoking and body cooling exert their effect upon reactive hyperemia via the sympathetic nervous system rather than through the direct action of nicotine or other circulating substances upon the blood vessels. This indication is supported particularly by the studies of patients with unilateral lumbar sympathectomies, who responded to the stimuli in the unsympathectomized foot but not in the sympathectomized foot. In this connection, in simultaneous studies on both feet Landowne and Katz[13] have shown that the blood flow in an extremity is not significantly affected by performing a reactive hyperemia measurement in the contralateral limb. We also observed on one patient (subject 20) that a unilateral sympathectomy resulted in an increased reactivity in the opposite extremity as compared with its presympathectomy responses.

## Summary

The effects of tobacco smoking and of body cooling on the increase in total blood flow that follows a period of ischemia (reactive hyperemia blood flow) of the foot were studied by venous occlusion, water plethysmography.

In 15 of 27 warm (83 F.) and 6 of 14 cool (68 F.) room experiments, the smoking of 2

cigarettes decreased the reactive hyperemia blood flow of the foot. In 14 of 17 studies, cooling the environment from 83 to 68 F. definitely decreased reactive hyperemia blood flow of the foot and appeared to be a more consistent stimulus than smoking in reducing reactive hyperemia. These studies also demonstrated that smoking and body cooling may have additive effects in reducing reactive hyperemia.

Experiments on patients with sympathectomized limbs showed that the above observed responses were mediated through the sympathetic nervous system. This was confirmed by the study of patients with unilateral sympathectomy who showed no decrease in reactive hyperemia blood flow in the sympathectomized foot during smoking but a definite decrease in the concomitantly studied unsympathectomized foot during smoking.


### Summario in Interlingua

Le effecto de fumar tabaco e de frigidar le corpore super le augmento del fluxo de sanguine total que occurre post un periodo de ischemia (fluxo sanguinee de hyperemia reactive) esseva studiate in le pede per medio de hydroplethysmographia sub conditiones de occlusion venose.

In 15 ex 7 experimentos in ambientes a temperatura elevate (83 F) e in 6 ex 14 experimentos in ambientes a temperatura reducite (68 F), le fumar de 2 cigarettas reduceva le fluxo de sanguine per hyperemia reactive in le pede. In 14 ex 17 experimentos, reducer le temperatura del ambiente ab 83 a 68 F ffectuava un definite reduction del fluxo sanguinee per hyperemia reactive in le pede. Il pareva que reducer le temperatura esseva plus constante que fumar tabaco in su effecto depressori super le hyperemia reactive. Le studios etiam indicava que fumar tabaco e frigidar le corpore exerce possibilemente effectos additive super le hyperemia reactive.

Experimentos in patientes con extremitates sympathectomisate monstrava que le supramentionate responsas es mediate per le systema nervose sympathic. Isto esseva confirmate per le studio de patientes con sympathectomia unilateral in qui fumar tabaco resultava in nulle reduction del fluxo sanguinee per hyperemia reactive in le pede sympathectomisate sed (in observationes concomitante) un definite reduction de ille fluxo in le pede non sympathectomisate.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# Congenital Complete Atrioventricular Block: Problems of Clinical Assessment

*By* Milton H. Paul, M.D., Abraham M. Rudolph, M.D., and Alexander S. Nadas, M.D.

The diagnosis of congenital complete atrioventricular block usually offers little difficulty. There remains, however, the problem of interpreting certain clinical findings, including systolic and diastolic murmurs and cardiomegaly, which are sometimes falsely suggestive of an associated congenital heart lesion. The clinical, radiologic, and electrocardiographic findings in 27 children with congenital complete heart block have been analyzed in terms of the hemodynamic abnormalities found at cardiac catheterization in 12 of these patients.

THE diagnosis of congenital complete atrioventricular block usually offers little difficulty. It requires only electrocardiographic verification of the mechanism of an abnormally slow heart rate that has been recognized in utero or early infancy and has occurred without any known toxic or infectious etiology. There frequently remains, however, the problem of the interpretation of clinical findings that are suggestive of an associated congenital cardiac lesion. Auscultation, in particular, has long been confusing, and it has been a common view that the systolic murmur heard in most patients with congenital heart block is indicative of a ventricular septal defect. Earlier studies also suggested that an underlying structural defect, usually in the ventricular septum, was responsible for the interruption in normal atrioventricular conduction.[1, 2] More recently, Campbell and Thorne[3] and Wood[4] have demonstrated that this relationship has undoubtedly been overemphasized.

The purpose of this communication is to present the clinical and hemodynamic findings in a group of children with congenital complete atrioventricular block and to analyze certain perplexing aspects of the clinical profile in relation to the hemodynamic abnormalities.

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## Material and Methods

Clinical, electrocardiographic, and radiologic examinations are available in 27 children, observed at the Children's Medical Center during the past 8 years (1949-57). These patients had electrocardiographic evidence of complete heart block without history of associated infection (diphtheria, rheumatic fever, virus) or intoxication (digitalis).

Phonocardiograms with simultaneous electrocardiograms or pulse tracings were obtained on selected patients by means of a dual channel photographic oscillograph. Right heart catheterization according to methods previously described[5] was performed in 12 of these patients with special attention directed to the detection of small left-to-right shunts. In 3 patients 2 intracardiac catheters were inserted to provide simultaneous blood sampling from the superior vena cava or right atrium and the main pulmonary artery, and in all patients multiple blood samples were obtained from the superior vena cava, right atrium, right ventricle, and pulmonary artery. In the children on whom ventilatory measurements and oxygen consumption could not be obtained the cardiac outputs were calculated on the basis of an assumed resting oxygen consumption of 180 ml. per minute per M.$^2$

## Results

*Clinical Profile.* The age of these patients (16 male and 11 female) ranged from 5 months to 14 years. In 2 complete atrioventricular block was suspected in utero by the obstetrician. In 12 additional instances the diagnosis was made within the first few months of life and in the remainder, under the age of 4 years.

Two children with definite cyanotic congenital heart disease will not be further discussed,

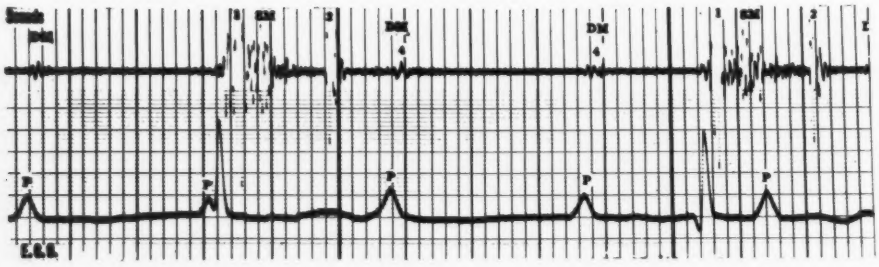

FIG. 1. Phonocardiogram (mid-left sternal) in a patient with no demonstrable left-to-right shunt on cardiac catheterization, illustrating prominent fourth heart sounds due to atrial systole.

since in the cyanotic patient with complete congenital heart block the presence of significant congenital heart disease cannot reasonably be doubted. The clinical profile is therefore based on an analysis of the findings in the remaining 25 acyanotic patients, and this group is homogeneous only in terms of the presence of complete atrioventricular block.

Twenty patients had completely normal exercise tolerance and 5 manifested varying degrees of easy fatigability. One of the latter eventually developed congestive heart failure. Respiratory tract infections were reported to be more frequent than usual in 8 patients. It is particularly noteworthy that in this entire group of children, representing approximately 180 patient years of complete heart block, there was no single bona fide episide of an Adams-Stokes attack. Physical development was usually normal although 5 patients were slightly underdeveloped in height or weight.

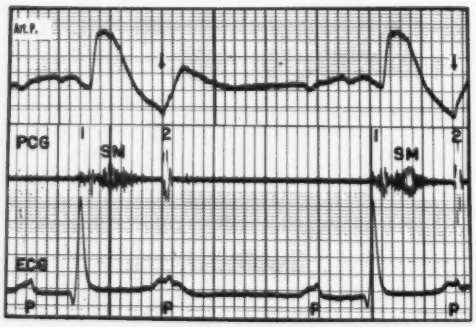


FIG. 2. Carotid artery tracing above and phonocardiogram (mid-left sternal) below from a patient with no demonstrable intracardiac left-to-right shunt. The systolic ejection murmur (*SM*) has a peak intensity near midsystole and ends well before the second sound.

Jugular venous pulsations showed prominent cannon "a" waves but were otherwise normal. The systolic blood pressure ranged from 85 to 120 mm. Hg (average 110), the diastolic blood pressure from 30 to 70 mm. Hg (average 54), and the pulse pressure from 35 to 100 mm. Hg (average 56).

Auscultation revealed that the first heart sound was frequently variable in intensity from beat to beat; the second heart sound was normally split, and of somewhat increased intensity. A distinct third heart sound was heard at the apex in 12 patients. A fourth heart sound was not heard with certainty but was identifiable in the phonocardiograms (fig. 1).

A systolic murmur of at least grade II intensity was heard in all but 1 of the 25 patients, and in 23 it was grade III or louder. This murmur (figs. 1 and 2) was usually of medium or high frequency, described as rough or blowing, generally occurring in the first two thirds of systole, and was heard best at the apex or lower left sternal border. Transmission was usually toward the apex and mid-left sternal border.

A diastolic murmur was noted in 22 patients, and in 19 it was of grade II or II intensity. The diastolic murmur (fig. 3 consisted of medium or low frequency vibrations, sometimes described as rumbling in quality. It was heard shortly after the second heart sound and was maximal at the apex or lower left sternal border. A third hear

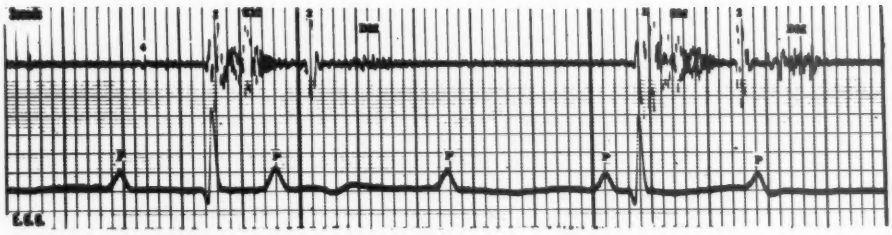

FIG. 3. Phonocardiogram (apex), same patient as figure 1. Diastolic murmur (*DM*) with medium and low frequency components starting shortly after second sound. Note the markedly increased intensity of the diastolic murmur in the second beat when atrial contraction (*P*) coincides with the early diastolic murmur.

sound was sometimes the initial vibration of this diastolic murmur, but more often the third sound appeared to be enveloped by the murmur. Notable in some patients was the variable intensity (fig. 3) of the diastolic murmur from beat to beat.

Radiologic examinations, including fluoroscopy, revealed cardiomegaly in 19 of the 25 acyanotic patients. Left ventricular enlargement was present in 16 patients (fig. 4) and in 11 of these some additional right ventricular enlargement was also evident. Left atrial enlargement was present in 10 patients. In only 3 patients was the pulmonary vasculature considered definitely increased, and in each a left-to-right shunt was subsequently proved at catheterization.

The electrocardiograms revealed an average ventricular rate of 54 per minute (range 42 to 85) and an average atrial rate of 112 per minute (range 74 to 180). A normal QRS axis (0° to 90°) was present in 14 patients, right axis deviation in 4 patients, and left axis deviation in 3 patients. Right atrial hypertrophy, as evidenced by p-pulmonale, was present in 8 children. The QRS complexes were of normal duration (0.04 to 0.08 second) in all but 1 patient who had a pattern of complete left bundle-branch block. Characteristic of the group was some tendency to left ventricular preponderance with a rS pattern and deep S in the right precordial lead ($V_1$) and a qRs pattern with tall R in the left precordial leads ($V_5$ and $V_6$). Only 4 patients had an rsR′ complex resembling incomplete right bundle-branch block. Cardiac catheterization was performed in 3 of the latter 4 patients, and in each an atrial septal defect was demonstrated.

*Catheterization Studies.* Twelve of the 25 acyanotic patients were studied by right heart catheterization because the clinical findings (hyperactive apical impulse, cardiac enlargement, systolic and diastolic murmurs) were initially suggestive of an associated left-to-right shunt. In 8 of these patients, however, no intracardiac shunts were demonstrable. Of the remaining 4 patients, 3 had left-to-right shunts at the atrial level, and 1 at the pulmonary artery level.

The pertinent hemodynamic data for the 8 patients without demonstrable intracardiac shunts are presented in table 1. The pressure tracings from this group indicate normal right atrial mean pressures, slightly elevated right ventricular (30 to 65 mm. Hg) but normal end-diastolic (3 to 8 mm. Hg.) pressures, and slightly elevated mean pulmonary artery (12 to 23 mm. Hg) and mean pulmonary "capillary" pressures (8 to 14 mm. Hg). Giant "a" waves (cannon waves) were always recorded in right atrial pressure tracings (fig. 5) if atrial systole occurred at a time when the tricuspid valve was closed. A small (15 mm. Hg or less) systolic pressure gradient across the pulmonary valve was demonstrated in 3 patients.

In all but 1 patient (no. 5) the systemic arteriovenous difference and the calculated systemic blood flow were within the normal resting range. The calculated stroke volume, however, was considerably increased (63 to

TABLE 1.—*Cardiac Catheterization Findings in Eight Patients with Congenital Complete Atrioventricular Block and No Demonstrable Left-to-Right Shunt*

| Patient | Age (years) | Ventricular rate (per min.) | Systemic arterial (mm.Hg) | Right ventricle (mm.Hg) | Pulmonary artery (mm.Hg) | Mean Pulmonary "capilllary" (mm.Hg) | Arteriovenous Oxygen difference (ml./$O_2$/100 ml.) | Oxygen consumption (ml/min./M.²) | Cardiac Cardiac index (L./min./M².) | Stroke index index (ml./M²) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 8/12 | 45 | 96/39 | 36/6 | 33/11 | 12 | 3.7 | * | 4.9 | 109 |
| 2 | 3 | 42 | 128/65 | 65/12 | 40/19 | 14 | 4.3 | * | 4.2 | 100 |
| 3 | 5 | 59 | 140/55 | 26/6 | 23/9 | 10 | 3.3 | 156 | 4.7 | 80 |
| 4 | 6 | 85 | 122/60 | 50/5 | 40/12 | 10 | 4.9 | 182 | 3.7 | 44 |
| 5 | 7 | 62 | 100/45 | 40/2 | 28/5 | 8 | 2.9 | 196 | 6.8 | 109 |
| 6 | 7 | 67 | 150/75 | 33/3 | 33/4 | 8 | 4.3 | 180 | 4.2 | 63 |
| 7 | 7 | 60 | 125/55 | 35/7 | 35/13 | 10 | 3.7 | 192 | 5.2 | 87 |
| 8 | 14 | 40 | 110/60 | 30/3 | 28/9 | 10 | 4.5 | 122† | 2.7 | 68 |

* Assumed at 180 ml. $O_2$/min./M.²
† Patient anesthetized.

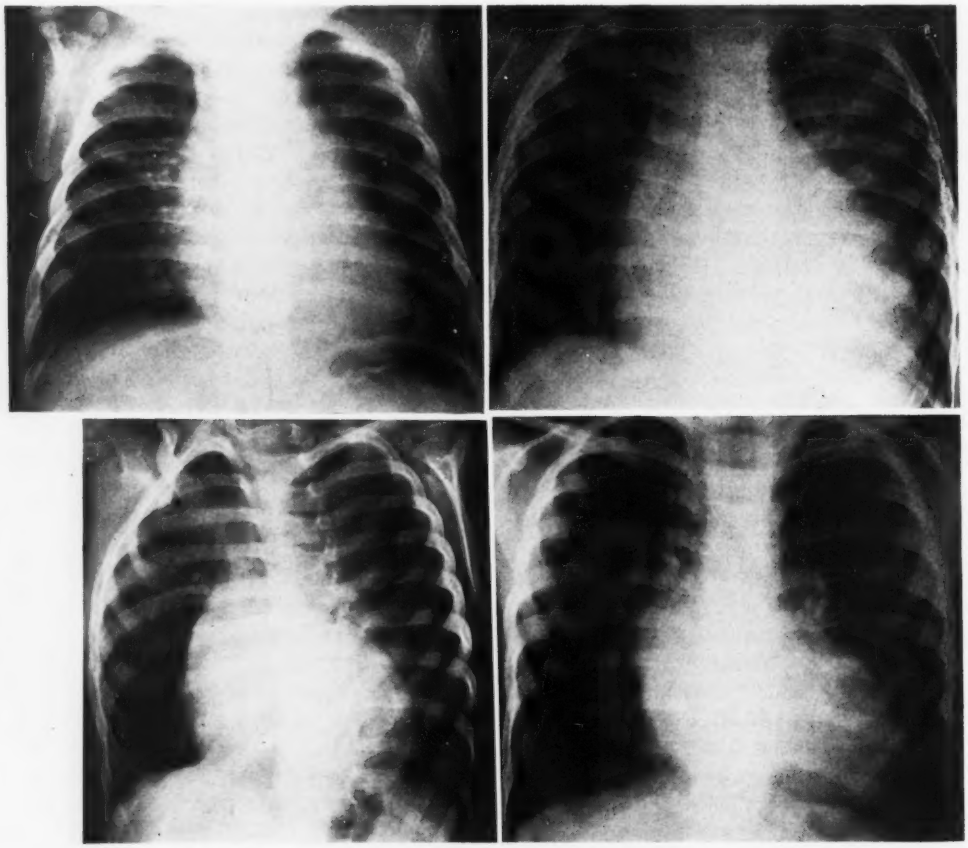

FIG. 4. Representative x-rays of 3 patients with congenital atrioventricular block and no evidence of associated atrial or ventricular septal lesions by cardiac catheterization. Note cardiomegaly and left ventricular dominance. *Top, left.* Patient E.G., 8 months. *Top, right.* Patient S.C., 3 years. *Bottom, left and right.* Left anterior oblique and anteroposterior x-rays of patient A.W., 5 years.

119 ml. per stroke per M.$^2$), except in 1 patient (no. 4) who had an unusually rapid ventricular rate (85 per minute) during the catheterization procedure. This increase in calculated stroke volume per square meter of body surface area (SV/M.$^2$) was the most consistent hemodynamic abnormality found at right heart catheterization in the patients without demonstrable intracardiac shunts.

## Discussion

Children with congenital complete atrioventricular block can present perplexing diagnostic and prognostic problems. In a few individuals an obvious cardiac defect such as cyanotic congenital heart disease or patent ductus arteriosus can be diagnosed readily by clinical methods. In others the findings are so minimal as to indicate at once the absence of any significant associated congenital heart disease. In a considerable number of patients, however, the clinical findings are highly suggestive of an associated intracardiac left-to-right shunt, specifically a ventricular or atrial septal defect, without being completely diagnostic of such. Right heart catheterization and long-term follow-up studies have failed to substantiate the clinical diagnosis of a septal defect in a considerable number of this latter group.

The present study suggests that certain clinical findings in complete heart block might be related directly to the altered hemodynamics associated with the slow ventricular rate. It would appear that the most significant physiologic consequences of the slow cardiac rate are the increased stroke volume, and the increased end-diastolic heart volume. The former may be responsible for some of the auscultatory findings and the latter for the frequently observed cardiomegaly.

A systolic murmur is almost always present in congenital complete heart block and its presence suggests the diagnosis of a ventricular or atrial septal defect in children. This murmur may equally well be explained by the large stroke volume and the associated high ejection velocity of the blood flow in complete heart block.[6, 7]

Phonocardiograms in our patients without demonstrable left-to-right shunts indicate that the systolic murmur is often restricted to the first half of systole and is high in frequency. These characteristics are suggestively similar to a form of "innocent systolic murmur" described by Wells[8] and can be related to increased turbulence in the blood stream at the time of rapid increase in the rate of blood flow. This murmur can be classified with the systolic murmurs heard in high cardiac output states, i.e., severe anemia, thyrotoxicosis, pregnancy, and the basal systolic murmur in atrial septal defects ("relative pulmonary stenosis").

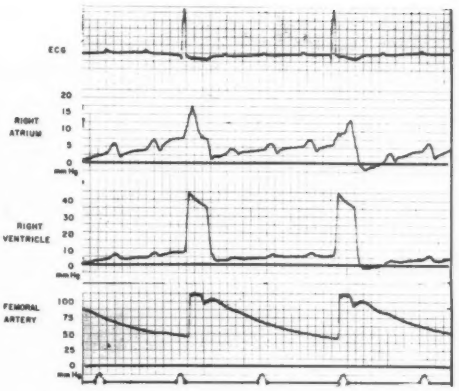


Fig. 5. Simultaneous electrocardiogram and pressure tracings from right atrium, right ventricle, and femoral artery illustrating the occurrence of giant "a" waves whenever atrial systole coincides with ventricular contraction.

A loud apical diastolic murmur was heard in 20 of the 25 children studied including each of the 8 patients who had no shunts demonstrated on right heart catheterization. The murmur (fig. 6) occurs early in diastole and is synchronous with the period of rapid ventricular filling. When the atria contract during this period, a summation effect can occur with a resultant increase in the intensity of the murmur (fig. 3).

The mechanism of this diastolic murmur in complete heart block may again be related to a slow cardiac rate and the resultant increased stroke volume. Although the total diastolic period is prolonged in bradycardia, the duration of the rapid ventricular filling

FIG. 6. Phonocardiogram and apexcardiogram from a patient with no demonstrable left-to-right shunt illustrating a low-frequency diastolic murmur beginning almost immediately after the second sound and enveloping a third heart sound during the period of rapid ventricular filling.

period is relatively constant over a wide range of heart rates. In 5 patients with congenital complete heart block (mean ventricular rate 42 per minute) the duration of the rapid ventricular filling period as estimated from the phonocardiogram ($S_2$ to $S_3$ interval) was 0.12 to 0.14 second. In 4 patients with tachycardia (mean ventricular rate 130 per minute) this period ranged from 0.11 to 0.13 second.

In complete heart block the abnormally large stroke volume that traverses the atrioventricular valves during early diastole may result in a high blood flow velocity, increased turbulence, and a diastolic murmur. A similar hypothesis of increased blood flow traversing a normal valve orifice has been advanced as the mechanism of the apical diastolic rumble in large left-to-right shunts ("relative atrioventricular valve stenosis").

Rytand[9] has described a diastolic apical murmur related to atrial activity in elderly patients with heart block. In the adult patients, as in the children reported here, the murmur was loudest early in diastole whenever atrial systole more or less coincided with the rapid diastolic filling period. It was postulated that after the atriventricular valves have been floated nearly together by early diastolic ventricular filling they constitute a relatively narrowed orifice for the continuing and accelerated (atrial contraction) transvalvular blood flow. The murmur disappears or is replaced by short atrial contraction sounds in late diastole (fig. 3) because the transvalvular blood flow has markedly decreased.

It should be clearly appreciated that other possible origins of these murmurs have not been definitely excluded even in those patients with essentially normal findings on right heart catheterization. Organic mitral valve lesions, possibly in association with endocardial fibroelastosis, are not completely excluded even though the pulmonary "capillary" pressures were only minimally elevated. Furthermore, a small septal defect could possibly not be detected because of the limitation of oxygen saturation methods in measuring small left-to-right shunts.

The radiologic and electrocardiographic findings in children with congenital complete heart block must similarly be interpreted with caution in regard to the diagnosis of an associated intracardiac lesion. In our study slight or moderate cardiomegaly was a frequent finding, occurring in 19 of the 25 acyanotic patients. It is general clinical experience that cardiac enlargement is common with bradycardia in adults,[10] and thus cardiomegaly might be expected in complete heart block even in the absence of any associated congenital heart lesion. It has also been demonstrated that experimental induction of complete heart block in the dog[11] frequently results in generalized cardiac enlargement and myocardial hypertrophy. Fortunately, the status of the pulmonary vasculature provides a relatively reliable finding in assessing this group for associated congenital heart lesions. The pulmonary vasculature was described as normal by the roentgenologist in each of the 8 patients without demonstrable left-to-right shunts on catheterization, whereas 3 of the 4 patients with left-to-right shunts had radiologic evidence of pulmonary vascular engorgement. The electrocardiogram is invaluable in establishing the diagnosis of congenital complete heart block. In addition considerable information can probably also be derived from the QRS complex, despite the fact that the conduction pathway is not intact. In contrast to acquired complete heart block in adults where over half of th

patients have idioventricular QRS complexes,[12] the electrocardiogram in congenital complete heart block almost always has a QRS complex that is supraventricular in form.[3, 13] In 24 of our 25 acyanotic patients the QRS complexes were of normal duration (0.04 to 0.08 second) and supraventricular in form. This finding would indicate that the dominant impulse center is located above the bifurcation of the bundle of His, and that the excitatory process propagates through the ventricular myocardium in a relatively normal sequence. Under these circumstances the usual criteria for ventricular hypertrophy should be applicable. Right ventricular hypertrophy was present in only 1 of the 25 acyanotic patients. Left ventricular hypertrophy was noted in 8 patients; cardiac catheterization in 3 of these did not disclose any significant associated congenital heart lesion. Incomplete right bundle-branch block was diagnosed in 4 patients; catheterization in 3 of this group demonstrated an atrial septal defect. These electrocardiographic data, although limited, suggest that left ventricular hypertrophy patterns are not uncommon in congenital complete heart block and that incomplete right bundle-branch block might possibly indicate the presence of an associated septal defect.

## Summary

The clinical, radiologic, and electrocardiographic features of congenital complete atrioventricular block have been reviewed in 27 infants and children, and cardiac catheterization was performed in 12 of these patients.

In this group certain clinical findings including a hyperactive apical impulse, prominent systolic and diastolic murmurs, and cardiomegaly are frequently suggestive of an associated congenital cardiac lesion with a left-to-right shunting of blood. Eight of the 12 patients studied by cardiac catheterization had no demonstrable congenital cardiac lesion except complete heart block, despite the presence of the above findings. In the remaining 4 patients with left-to-right shunts demonstrated by cardiac catheterization the only reliable sign of the associated congenital cardiac lesion was the radiologic demonstration of an engorged pulmonary vasculature.

It is suggested that the difficulty in interpreting certain auscultatory findings in patients with complete congenital heart block is related to the large stroke volume associated with the slow heart rate. This results in a high velocity of blood flow through the semilunar and atrioventricular valves and can produce murmurs suggesting functional stenosis. The large stroke volume is also associated with a large end-diastolic heart volume, probably leading to cardiomegaly.

Since long-term studies indicate that the prognosis in complete congenital heart block is dependent primarily on the nature of the associated congenital cardiac lesion that may be present, it is important to establish a correct anatomic diagnosis of any septal defect with a view to surgical correction when indicated.

## Summario in Interlingua

Le aspectos clinic, radiologic, e electrocardiographic de congenite bloco atrioventricular complete esseva revidite in 27 infantes e juveniles. Catheterisation cardiac esseva interprendite in 12 de illes.

In iste gruppo certe constatationes clinic—incluse un hyperactive impulso apical, prominente murmures systolic e diastolic, e cardiomegalia—es frequentemente indicios de un associate lesion cardiac congenite con derivation sinistro-dextere de sanguine. Octo del 12 patientes studiate per catheterisation cardiac habeva nulle congenite lesion cardiac excepte le complete bloco cardiac, ben que le supra-listate indicios esseva presente. In le altere 4 patientes con derivationes sinistro-dextere demonstrate per catheterisation cardiac, le sol convincente signo de un associate lesion cardiac congenite esseva le demonstration radiologic de un turgide vasculatura pulmonar.

Es exprimite le opinion que le difficultate del interpretation de certe constatationes auscultatori in patientes con congenite bloco cardiac complete es relationate al grande volumine per pulso que es associate con le basse frequentia cardiac. Isto resulta in un alte

velocitate del fluxo de sanguine a transverso le valvulas semilunar e atrioventricular e pote producer murmures que pare indicar stenosis functional. Le grande volumine per pulso es etiam associate con un grande volumine cardiac termino-diastolic, e isto resulta probabilemente in cardiomegalia.

Proque studios a longe vista indica que le prognose in congenite bloco cardiac complete depende primarimente del natura del possibilemente associate lesion cardiac congenite, il es importante establir un correcte diagnose anatomic con respecto al presentia de un defecto septal e corriger lo chirurgicamente si un tal manovra es indicate.

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## THE METHODS OF SCIENCE

J. Arthur Thomson

British: professor of natural history, editor and author; 1861-1933

In any scientific inquiry the first step is to get at the facts, and this requires precision, patience, impartiality, watchfulness against the illusions of the senses and the mind, and carefulness to keep inferences from mingling with observations. The second step is accurate registration of the data. A third step is arranging the data in workable form. The fourth step is when a whole series of occurrences is seen to have a uniformity, which is called their law.—*The Outline of Science,* Vol. 4, p. 1165. From *Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources.* Vol. I, Boston, The Beacon Press, 1952.

# Effect of Atherosclerosis and Age upon the Serum Mucoprotein and Hexosamine Levels in Man

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Serum mucoprotein and hexosamine levels have been determined in atherosclerotic, nonatherosclerotic, and young male subjects. A highly significant elevation of both fractions was noted in the atherosclerotic group. Elevations due to aging were also obtained. It is suggested that these results are consistent with the view that arterial wall mucopolysaccharide depolymerization plays a role in the pathogenesis of human atherosclerosis.

CONSIDERABLE emphasis has been placed upon the role of lipid abnormalities in the pathogenesis of atherosclerosis, but little attention has been paid to the possible significance of deranged tissue metabolism. In many species, including man, the earliest atheromatous lesions are characterized by the subintimal accumulation of a mucoid material. These mucopolysaccharide deposits were described by Taylor[1] in 1953. Faber[2] suggested that such mucoid substances were directly concerned with the deposition of cholesterol in tissues, including the aorta, and this view was later expanded by Altshuler and Angevine.[3] The possible significance of altered mucopolysaccharide metabolism in the genesis of atherosclerosis was recently stressed by Wartman,[4] while Schwartz et al.[5] have demonstrated that similar histochemical abnormalities occur at the sites of aortic atheromatous lesions in the cholesterol-fed rabbit, together with an elevation of the serum hexosamine levels.

The ground substance of the arterial tree contains chondroitin-sulphuric acid compounds, but the presence of hyaluronate is in doubt.[6] Depolymerization or hydrolysis of these materials leads to an elevation within the serum of their component amino sugars. This will occur in rabbits after a solitary injection of testicular hyaluronidase[7] and after prolonged administration of the substance.[5] A similar elevation in the serum hexosamine levels of rats was produced by Schwartz and Gilmore[8] and in addition marked elevations of the serum mucoproteins were noted. These findings suggest that elevations of both the amino sugar and the serum mucoprotein fractions may be interpreted as reflecting a breakdown of mesodermal ground-substance mucopolysaccharides.

One might expect that, as the histochemical abnormalities of human atherosclerosis probably reflects changes in both the quantity and state of polymerization of arterial mucopolysaccharides, these alterations might be reflected by changes in the serum amino sugar and mucoprotein levels.

This paper describes the results of an investigation of the effects of age and atherosclerosis on the serum hexosamine and serum mucoprotein levels in man.

## MATERIALS AND METHODS

Three groups of subjects were investigated. The first group consisted of 24 normal male medical students with ages varying from 19 to 35 years (average 25 years). The second group consisted of 23 atherosclerotic male patients with an age range of 40 to 72 years (average 56 years). Most of these patients were suffering from angina of effort; 3 had a myocardial infarction 6 months or more prior to investigation from which they had clinically recovered. The third group of 16 were clinically nonatherosclerotic men with an age range of 37 to 71 years (average 52 years). The ages of these latter individuals were comparable with those of the atherosclerotic group. These age controls were normotensive, without clinical or electrocardiographic evidence of myocardial ischemia, and judged to be free from atherosclerosis on clinical assessment. Single venous blood samples were collected from the median cubital veins,

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TABLE 1.—*Changes with Atherosclerosis and Age in the Serum Mucoprotein and Hexosamine Levels*

| Atherosclerotic subjects | | | Age controls | | | Young controls | | |
|---|---|---|---|---|---|---|---|---|
| Age (yrs.) | Serum hexosamine (mg./100 ml.) | Serum mucoprotein (mg./100 ml.) | Age (yrs.) | Serum hexosamine (mg./100 ml.) | Serum mucoprotein (mg./100 ml.) | Age (yrs.) | Serum hexosamine (mg./100 ml.) | Serum mucoprotein (mg./100 ml.) |
| 40 | 116 | 112 | 37 | 99 | 107 | 19 | 85 | 79 |
| 40 | 131 | 162 | 37 | 103 | 95 | 20 | 102 | 77 |
| 46 | 113 | 141 | 37 | 92 | 87 | 20 | 94 | 88 |
| 48 | 112 | 100 | 40 | 90 | 96 | 20 | 95 | 85 |
| 49 | 116 | 130 | 42 | 97 | 87 | 20 | 92 | 85 |
| 49 | 99 | 152 | 47 | 89 | 105 | 20 | 86 | 77 |
| 49 | 125 | 136 | 49 | 92 | 86 | 20 | 94 | 108 |
| 50 | 115 | 143 | 49 | 95 | 77 | 21 | 90 | 107 |
| 50 | 125 | 150 | 51 | 100 | 110 | 21 | 95 | 75 |
| 53 | 111 | 143 | 53 | 93 | 95 | 22 | 93 | 84 |
| 53 | 112 | 118 | 55 | 108 | 93 | 22 | 94 | 73 |
| 55 | 118 | 89 | 56 | 105 | 99 | 23 | 94 | 92 |
| 58 | 114 | 164 | 68 | 92 | 77 | 24 | 81 | 69 |
| 58 | 147 | 181 | 70 | 117 | 113 | 26 | 86 | 84 |
| 59 | 110 | 127 | 71 | 87 | 93 | 26 | 100 | 79 |
| 60 | 121 | 138 | 71 | 95 | 110 | 27 | 86 | 103 |
| 63 | 117 | 129 | — | — | — | 29 | 88 | 98 |
| 63 | 127 | 229 | — | — | — | 29 | 99 | 105 |
| 66 | 125 | 120 | — | — | — | 29 | 77 | 59 |
| 67 | 118 | 192 | — | — | — | 31 | 102 | 92 |
| 70 | 117 | 145 | — | — | — | 31 | 90 | 84 |
| 70 | 132 | 123 | — | — | — | 32 | 98 | 78 |
| 72 | 117 | 154 | — | — | — | 33 | 91 | 100 |
| — | — | — | — | — | — | 35 | 100 | 98 |
| Means | | | | | | | | |
| 56 | 119.0 | 142.5 | 52 | 97.1 | 95.6 | 25 | 92.2 | 86.6 |
| S.E.$_M$ | | | | | | | | |
| | | ±2.00 | ±6.33 | ±1.99 | ±2.81 | | ±1.33 | ±2.61 |
| *$p$ | <0.001 | <0.001 | | <0.05 | <0.02 | | — | — |

* Probability was assessed by the student's t test, except in the case of the mucoprotein levels in atherosclerosis where a Fisher-Behrens test was applied, because of a difference in the standard errors of the 2 groups.

and the sera were obtained after centrifugation at 3,000 r.p.m. for 10 minutes. The biochemical determinations were performed without knowledge of the source of the samples.

*Serum hexosamine* levels were determined by the method of West and Clarke[9] on 0.2 ml. of serum. The pink color developed was read in a Unicam S.P. 600 spectrophotometer at 540 mu. Serum hexosamine was expressed as mg. per 100 ml. of glucosamine with a standard of glucosamine hydrochloride.*

*Serum mucoprotein* was determined according to the method of Winzler et al.[10] with certain modifications. Only 0.2 ml. of serum was used and the mucoprotein was determined as protein by the sensitive method of Lowry et al.[11] with the Folin Ciocalteau reagent. Mucoprotein was then expressed as mg. per 100 ml. of serum in terms of its protein content using human albumin standards. The blue color developed was again read in a Unicam S.P. 600 spectrophotometer at 760 mu.

## RESULTS

An elevation of the serum mucoprotein with age was found, the mean level in the student group being 86.6, while the mean of the nonatherosclerotic age controls is higher (95.6) ($p < 0.02$). A greater difference between the atherosclerotic and nonatherosclerotic groups can be readily seen from table 1, where the mean level for the former is 142.5, and for the latter 95.6. This elevation of the serum mucoprotein level in atherosclerosis above the level in a nonatherosclerotic group of comparable age is highly significant ($p < 0.001$). Similar results were obtained with respect to serum hexosamine differences. The increase in the mean level with age from 92.2 to 97.1 in the nonatherosclerotic age controls is significant ($p < 0.05$). In the atherosclerotic group the mean level (119.0) is significantly higher than the mean level of the age control group ($p < 0.001$). From a comparison of the mucoprotein and hexosamine values it can be seen that the degree of change is greater with the former than the latter.

## DISCUSSION

The findings of an increase in metachromatic staining material in the lesions of human atheroma by Taylor[1] suggested to the authors that mesodermal ground-substance changes may be involved in the pathogenesis of atherosclerosis. It has further been demonstrated that similar histochemical changes occur in, and subjacent to, atheromatous lesions in cholesterol-fed rabbits, together with a concomitant elevation of the serum amino sugar

*Glucosamine hydrochloride, kindly supplied by Nutritional Biochemical Corporation, Cleveland, Ohio.

levels.[5] These findings, histochemical and biochemical, both suggest that ground-substance mucopolysaccharide depolymerization occurs in the pathogenesis of atheroma in cholesterol-fed rabbits. A similar elevation in the serum amino sugar levels in cholesterol-fed rabbits has been reported.[12]

Accentuation of the depolymerization by testicular hyaluronidase has been shown to increase atherogenesis in hypercholesterolemic rabbits.[5, 13, 14] Contrasted with this finding is the inhibition of atherogenesis in cholesterol-fed rabbits with cortisone.[15–17]

In this paper, biochemical evidence of an increased breakdown of ground-substance mucopolysaccharides in male patients with clinical evidence of atherosclerosis is provided by the finding that both the serum mucoprotein and hexosamine levels in the atherosclerotic group are significantly elevated above those of the nonatherosclerotic age controls (table 1) ($p < 0.001$).

In order to determine more exactly the significance of serum mucoprotein elevations, Schwartz and Gilmore[8] produced an in vivo enzymatic depolymerization of ground-substance mucoids in rats with testicular hyaluronidase. Marked elevations in both the mucoprotein and hexosamine fractions were recorded. Similar elevations in the serum hexosamine levels of rabbits have been reported by this specific enzymatic depolymerization of ground substance.[5, 7] One may therefore interpret some elevations of both these fractions as reflecting a breakdown of connective tissue mucopolysaccharides. Further support for this interpretation is found in the elevations of the serum glycoproteins that have been reported in the so-called collagen diseases, rheumatic fever,[18] and in the rheumatic group of disorders.[19] The similarity between the biochemical findings in atherosclerosis as reported in this study and those found in the collagen diseases is striking, though the changes in atherosclerosis are of lesser degree. Similar observations on the glycoprotein levels in atherosclerosis have been recently reported by Antonini and Salvini[20] while this work was in progress.

Metachromatically staining intercellular substance is probably involved as a precursor in the formation of reticulum and collagen fibrils in granulation tissue.[21–24] It is possible therefore that the extensive intimal and subintimal fibrosis that characterizes established atheromatous lesions in both the experimental animal and in human subjects is derived from the metachromatically staining mucopolysaccharides seen in similar sites at an earlier stage in these lesions. Of related interest is the observation of Watson and Pearce[25] that in pretibial myxedema progressive fibrosis is associated with diminution of tissue mucopolysaccharide concentration.

If such a process of connective tissue ground-substance depolymerization is of significance in atherogenesis, it is of interest to note the low mucoprotein levels in an ethnic group, the nomadic Australian aborigine, which has a low incidence of atheroma. The low serum glycoprotein level of this group is contrasted with the higher level that occurs in a group of urban aborigines, whose levels do not differ significantly from those of normal white Australians.[26]

A trend toward an increase with aging in both the glycoprotein fractions is not surprising. Atherosclerosis has a greater incidence in the older age groups, and an increased ground-substance catabolism due to age would possibly help account for this. The possibility of some occult atherosclerosis in the control group cannot be excluded in a community such as this, in which atherosclerosis is becoming a common disorder.

The present findings suggest that depolymerization of the mesodermal ground substance plays a role in the pathogenesis of human atherosclerosis. However, whether it is basic to the pathology of atherosclerosis or merely occurs secondary to some other process, such as hypercholesterolemia, still remains to be determined.

## Summary

Highly significant elevations of both the serum mucoprotein and hexosamine levels in atherosclerosis are reported. There is also a

trend for an increase in both these fractions as the result of aging.

These findings are interpreted as reflecting an increased depolymerization of connective tissue ground-substance mucopolysaccharides.

It is suggested that connective tissue ground-substance breakdown plays a role in the pathogenesis of atherosclerosis, possibly as a precursor to fibrogenesis.

### Acknowledgment

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### Summario in Interlingua

Es reportate significativissime elevationes del nivellos seral de mucoproteina e de hexosamina in patientes con atherosclerosis. Il existe etiam un tendentia accrescitori in ambe iste fractiones como effecto de avantiamento del etate.

Iste constatationes es interpretate como reflexion de un augmentate dispolymerisation del mucopolysaccharidos in le substantia basal del histos conjunctive.

Es suggerite que discomposition del substantia basal in histos conjunctive ha forsan un rolo in le pathogenese de atherosclerosis e es possibilemente un precursor de fibrogenese.

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**Higginbotham, A. C.: Intraocular Arterial Homotransplants for Studying Atherosclerotic Lesion Regression.** Science **125**: 554 (March 22), 1957.

A technic is described for the use of intraocular arterial homotransplantation for the study of spontaneous or experimentally induced atherosclerosis in animals. A portion of an artery is excised and a small piece of normal or atherosclerotic vessel is implanted through an incision into the anterior eye chamber. The transplant is moved to the opposite side across the chamber and wedged between the cornea and iris, with the intimal surface facing outward. At a selected time, a host animal may be sacrificed and histologic section may be studied to determine the nature and degree of both structural and biochemical changes. The adventitia of the transplants becomes attached to the anterior surface of the host's iris by fibroconnective tissue in less than 8 days. In addition, the thickened intima of atherosclerotic transplants becomes extensively vascularized, but that of the normal transplants does not. Thus far, transplants have been in place for 6 months, and this would seem to permit the use of these animals in relatively long-term nutritional and pharmacologic experiments.

Waife

# Sodium Chloride Excretion Following Salt Loading in Hypertensive Subjects

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Patients with essential hypertension show an altered renal excretory response to sodium chloride loading. Hypertensive patients acutely eliminate a greater proportion of a salt and water load than do normotensive subjects. This renal abnormality appears to be due to an augmented tubular rejection of sodium chloride and water. This study further defines the nature and extent of this alteration in electrolyte and water metabolism.

A PREVIOUS study[1] confirmed the observations of others[2-9] that hypertensive patients excrete more of a parenterally administered sodium chloride load than do normal subjects, and demonstrated that this abnormality was not related to measurable increases in glomerular filtration rate or tubular load of sodium chloride. The present report examines the excretion of sodium chloride and water during the 36-hour period before, during, and after the load of sodium chloride in hypertensive and normotensive subjects. It presents more specific information concerning whether (1) this difference in sodium chloride excretion can also be detected in the resting state before loading, (2) it is found in labile hypertensive patients at the time their blood pressure is normal, and (3) it is similar to the excretory response of patients with hyperadrenocorticism. The possible mechanisms of this excretory abnormality are critically analyzed in the light of these experiments and data available in the literature.

## METHODS

Ambulant patients on an unrestricted diet collected their urine from 6 p.m. the day before to 6 a.m. the day of the test. They ate their usual dinner the evening before but were instructed not to eat or drink afterwards. A second urine sample was collected from 6 a.m. to 9 a.m. the day of the test. At 8:50 a.m. they drank 450 ml. of water per 1.73 M.$^2$ body surface area, then at 9 a.m. were infused with 500 ml. per 1.73 M.$^2$ body surface area of 2.5 per cent sodium chloride at a rate of 8 ml. per 1.73 M.$^2$ body surface area per minute, the infusion lasting approximately until 10 a.m. At 10:30 the urine collection of the first load period ended, and at 12 noon the second load period was completed. Patients remained recumbent during these 2 periods. At 12 noon they ate a lunch calculated to contain 186 mg. of sodium.* They collected their urine from 12 noon to 6 p.m. and from 6 p.m. to 6 a.m. the following morning. Dinner the evening of the test consisted of a cup of tea, an egg, a piece of toast with jelly, and unsalted noodles. No other fluid was permitted. The sodium content of this meal was calculated to be 41 mg. The volume of each urine sample was measured and sodium and potassium concentrations were determined by flame photometry. The normal group (I) was composed of normotensive laboratory workers and ward patients. The hypertensive patients were divided according to their diastolic blood pressure at the time of testing as follows: group II (88 to 109 mm. Hg); group III (110 to 124 mm. Hg); and group IV (125 to 141 mm. Hg). Group V consisted of patients previously reported to have hypertension of 170/100 mm. Hg or more, but who were normotensive without treatment at the time of the test.

## RESULTS

*Rate of Sodium Chloride Excretion Before, During, and After Loading.* The mean hourly

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TABLE 1.—*Sodium Excretion of Individual Subjects*

| Patient no. | Blood pressure (mm. Hg) | Preload: 6 pm to 6 am (mEq /hr) | Preload: 6 am to 9 am (mEq /hr) | Load: 9 am to 12 noon mEq) /hr) | Postload: 12 noon to 6 pm (mEq /hr) | Postload: 6 pm to 6 am (mEq /hr) | Excretion of infused load: In 3 hrs. (%) | Excretion of infused load: In 21 hrs. (%) |
|---|---|---|---|---|---|---|---|---|
| I. Normotensive | | | | | | | | |
| 1 | 98/58 | 1.3 | — | 26.0 | 6.3 | 2.8 | 35 | 66 |
| 2 | 100/64 | 2.0 | 0.5 | 7.7 | — | 2.9 | 10 | — |
| 3 | 104/60 | 6.4 | 3.9 | 11.4 | 5.4 | 4.2 | 22 | 74 |
| 4 | 106/54 | 1.8 | 0.5 | 3.6 | 0.8 | 4.4 | 6 | 35 |
| 5 | 108/68 | 13.4 | 13.5 | 23.7 | 11.1 | 3.1 | 36 | 139 |
| 6 | 108/72 | 8.1 | 4.5 | 16.9 | 17.0 | 7.1 | 21 | 100 |
| 7 | 110/74 | 15.0 | — | 10.7 | 9.0 | 6.8 | 14 | 72 |
| 8 | 110/64 | 2.8 | 1.1 | 15.8 | — | — | 25 | — |
| 9 | 116/74 | 5.4 | 0.6 | 20.2 | — | 13.0 | 26 | — |
| 10 | 120/86 | 5.4 | — | 8.5 | 5.6 | 1.9 | 12 | 37 |
| II. Mildly hypertensive | | | | | | | | |
| 11 | 142/100 | 7.8 | 1.4 | 21.0 | 6.7 | 6.1 | 25 | 69 |
| 12a | 146/88 | 0.7 | 0.3 | 1.3 | 1.5 | 5.1 | 2.6 | 35 |
| 13a | 143/106 | 7.5 | 8.0 | 40.5 | 8.5 | 3.8 | 48 | 87 |
| 13b | 148/108 | 9.8 | 5.6 | 44.5 | 8.5 | 9.2 | 53 | 118 |
| 14 | 147/102 | 9.4 | 5.9 | 9.9 | 6.0 | 4.0 | 18 | 64 |
| 15 | 154/99 | 12.0 | 5.9 | 31.4 | 7.7 | 5.6 | 41 | 90 |
| 16 | 158/108 | 2.4 | 5.0 | 14.7 | 8.8 | 3.1 | 19 | 59 |
| 17 | 170/106 | 2.2 | 1.3 | 10.0 | 8.5 | 1.1 | 16 | 50 |
| 18 | 174/90 | 9.1 | — | 34.6 | — | 2.3 | 60 | — |
| III. Moderately severely hypertensive | | | | | | | | |
| 19 | 175/110 | 13.8 | 1.3 | 39.6 | 8.9 | 4.4 | 54 | 102 |
| 20a | 160/118 | 9.5 | 33.0 | 31.0 | 4.5 | — | 67 | 81 |
| 20b | 149/104 | 1.9 | 1.0 | 11.0 | 1.2 | 1.7 | 17 | 30 |
| 21a | 160/115 | 11.6 | 10.8 | 21.8 | 12.8 | 6.4 | 29 | 96 |
| 22 | 164/114 | 4.0 | 6.4 | 35.0 | — | — | — | — |
| 23a | 178/116 | 9.6 | 6.1 | 46.0 | 6.7 | 6.9 | 57 | 109 |
| 23b | 163/126 | 4.6 | — | 39.0 | 4.2 | 6.6 | 49 | 93 |
| 24 | 171/110 | 12.1 | 8.7 | 35.2 | 6.5 | 5.5 | 46 | 91 |
| 25a | 179/136 | 3.8 | 2.6 | 18.0 | 5.3 | 4.0 | 26 | 66 |
| 25b | 176/112 | 2.9 | 3.7 | 14.5 | 4.2 | 4.3 | 21 | 59 |
| 26 | 183/112 | 11.0 | 8.7 | 31.5 | 9.8 | 7.2 | 40 | 101 |
| 27 | 184/124 | 3.5 | 8.7 | 30.0 | 12.0 | 17.0 | 37 | 151 |
| 28 | 192/110 | 5.4 | 0.8 | 48.0 | 9.2 | 6.4 | 58 | 110 |
| 29 | 200/115 | 8.8 | 4.3 | 20.8 | 5.7 | — | 31 | — |

TABLE 1.—*Continued*

| Patient no. | Blood pressure (mm. Hg) | Preload: 6 pm to 6 am (mEq /hr) | Preload: 6 am to 9 am (mEq /hr) | Load: 9 am to 12 noon (mEq /hr) | Postload: 12 noon 6 pm to (mEq /hr) | Postload: 6 pm to 6 am (mEq /hr) | Excretion of infused load: In 3 hrs. (%) | Excretion of infused load: In 21 hrs. (%) |
|---|---|---|---|---|---|---|---|---|
| IV. Severely hypertensive | | | | | | | | |
| 30 | 201/136 | 8.3 | — | 101.0 | 12.0 | 6.4 | 141 | 208 |
| 31a | 206/128 | 5.5 | — | 30.8 | 9.1 | 9.3 | 52 | 144 |
| 31b | 206/130 | 12.2 | 7.6 | 24.9 | 6.1 | 6.9 | 42 | 108 |
| 32 | 212/134 | 3.5 | 2.8 | 24.4 | 2.8 | 11.3 | 34 | 105 |
| 33 | 235/144 | 7.9 | — | 28.9 | 4.8 | 5.2 | 43 | 93 |
| V. Labile hypertensive | | | | | | | | |
| 34 | 98/62 | 5.8 | 26.3 | 7.0 | 12.0 | 7.5 | 10 | 90 |
| 35 | 112/74 | 9.7 | 10.6 | 24.5 | 9.2 | 8.4 | 30 | 92 |
| 36 | 114/74 | 0.7 | 2.1 | 17.4 | 3.1 | 4.1 | 26 | 60 |
| 37 | 116/68 | 15.8 | 7.4 | 22.3 | 11.1 | 5.2 | 28 | 81 |
| 38 | 134/78 | 4.7 | 1.4 | 15.7 | 15.2 | 5.7 | 18 | 80 |
| 39 | 136/68 | 7.2 | 4.2 | 21.7 | 9.9 | 4.6 | 29 | 79 |
| 40 | 138/76 | 6.9 | 10.1 | 27.3 | 13.6 | 4.8 | 34 | 92 |
| 41 | 140/76 | 11.7 | 12.6 | 67.3 | 11.3 | 4.8 | 93 | 152 |
| VI. Hyperadrenocorticism | | | | | | | | |
| 42 (S.T., pre) | 116/71 | 7.9 | 7.0 | 28.4 | 19.7 | 8.0 | 39 | 138 |
| 42 (S.T., post) | 114/74 | 7.5 | 10.0 | 19.9 | 16.5 | 9.0 | 28 | 123 |
| 43 (R.G.) | 168/123 | 8.3 | 1.0 | 40.3 | 3.5 | 4.4 | 64 | 102 |

Data arranged according to ascending blood pressure in each group.

Duplicate experiments on the same patient indicated by a and b.

sodium excretion rates in both the overnight and in the early morning preload periods showed a slight progressive increase from group I to III (tables 1 and 3, and fig. 1). Group IV also showed a greater mean rate of sodium excretion than did the normotensive subjects. The mean overnight rate prior to test and on a self-selected diet was 6.2 mEq. per hour (normal) and 6.5, 7.9, and 7.2 mEq. per hour respectively in the groups with progressively greater blood pressure elevations. No statistical significance can be attached to differences between these values. The infusion of the salt load lasted approximately 1 hour and, in general, the urine collections of any one subject during the first and second 90-minute load period contained similar amounts of sodium in mEq. per hour except among patients in group IV, who showed a greater excretion rate in the first load period. These 2 load periods are therefore combined in the tables although group means are illustrated for each separate period in figure 1. In the load periods the groups can be distinguished more readily with mean sodium ex-

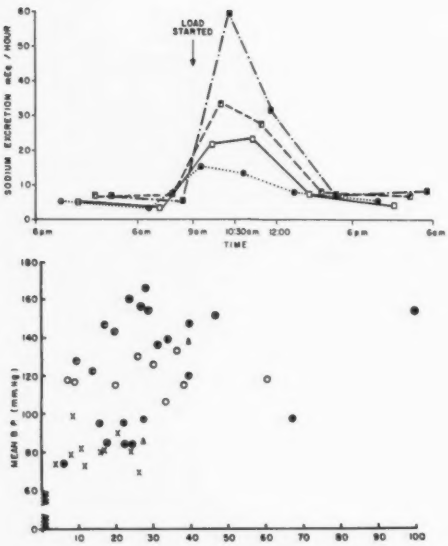


FIG. 1 *Top.* The mean sodium excretion of the normotensive (●), mildly (□), moderately severely (◩), and severely hypertensive (■) groups during the preload, load, and postload periods.

FIG. 2 *Bottom.* The relation of mean blood pressure to sodium excretion (mEq./hour *abscissa*) during the 3-hour load period (9 a.m. to 12 noon) in the normotensive (×), mildly (○), moderately severely (◐), severely (●), and labile hypertensive (⊗) subjects and in the 2 patients with hyperadrenalcorticism (△).

cretion rates of 14.5 mEq. per hour for the normal subjects and 20.7, 31.1, and 45.6 mEq. per hour for the hypertensive patients in groups II to IV, during the 3-hour load period. Individual variations were so great that differences between means were not statistically significant. Percentage excretion of the infused load during this load period rose directly in proportion to the mean blood pressure, from 20 in the normotensive to 66 in the severely hypertensive group (table 3). In figure 2, the correlation between sodium excretion under load and blood pressure is presented. There is considerable scatter ($r = 0.4$). Subtracting the basal or preload hourly sodium excretion did not improve the correlation.

The first postload period from 12 noon to 6 p.m., which began approximately 2 hours after the sodium chloride infusion ended, revealed

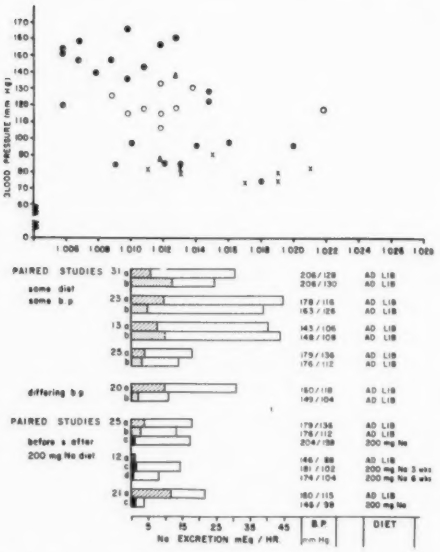


FIG. 3 *Top.* The relation of the mean blood pressure to the urinary specific gravity (*abscissa*) during the 3-hour load period. Symbols as in figure 2.

FIG. 4 *Bottom.* Effect of changes in blood pressure and in sodium content of the diet on sodium excretion following loading. *Cross-hatched* and *stippled bars,* 6 p.m. to 6 a.m. preload sodium excretion of patients on an ad lib. diet; *solid bars,* same period for subjects on a 200-mg. sodium diet; *open bars,* 9 a.m. to 12 noon 3-hour load period for all subjects. Patients numbered as in tables; a, b, c, and d refer to repeated tests on the same subject. Patients no. 21 and 25 were retested after 3 weeks on a 200-mg. sodium diet.

that the mean hourly excretory rates of sodium had returned almost to preload values. The normal group excreted sodium at the rate of 7.9 mEq. per hour; the others at 6.8, 7.8, and 6.8 mEq. per hour respectively. In the final postload period, 6 p.m. to 6 a.m., the mean levels of sodium excretion fell in all but the severely hypertensive group to below the values for the preload overnight collections. The mean cumulative sodium excretion over the entire 21-hour period, subsequent to initiating the intravenous load, was generally higher in the more severe grades of hypertension. In the entire 21-hour period, the various groups excreted from 67 to 133 per cent of the infused load. These calculations are based on

TABLE 2.—*Urine Volumes of Individual Subjects*

| Patient no. | Preload | | Load | Postload | |
|---|---|---|---|---|---|
| | 6 p.m. to 6 a.m. (ml./hr.) | 6 a.m. to 9 a.m. (ml./hr.) | 9 a.m. to 12 noon (ml./hr.) | 12 noon to 6 p.m. (ml./hr.) | 6 p.m. to 6 a.m. (ml./hr.) |
| I. Normotensive | | | | | |
| 1 | 92 | — | 190 | 58 | 82 |
| 2 | 41 | 18 | 48 | — | 26 |
| 3 | 44 | 31 | 60 | 28 | 22 |
| 4 | 18 | 5 | 28 | 4 | 26 |
| 5 | 52 | 48 | 164 | 47 | 39 |
| 6 | 75 | 29 | 95 | 64 | 109 |
| 7 | 62 | — | 54 | 86 | 28 |
| 8 | 50 | 11 | 82 | — | — |
| 9 | 92 | 7 | 231 | — | 98 |
| 10 | 30 | — | 38 | 26 | 18 |
| II. Mildly hypertensive | | | | | |
| 11 | 62 | 9 | 129 | 37 | 33 |
| 12a | 47 | 19 | 53 | — | 38 |
| 13a | 79 | 67 | 311 | 54 | 88 |
| 13b | 91 | 44 | 283 | 44 | 76 |
| 14 | 40 | 27 | 39 | 27 | 23 |
| 15 | 57 | 29 | 235 | 32 | 31 |
| 16 | 28 | 53 | 74 | 49 | 18 |
| 17 | 53 | 21 | 49 | 36 | 5 |
| 18 | 37 | — | 174 | — | 39 |
| III. Moderately severely hypertensive | | | | | |
| 19 | 79 | 18 | 240 | 50 | 47 |
| 20a | 91 | 91 | 355 | 31 | 67 |
| 20b | 48 | 16 | 83 | 20 | 13 |
| 21a | 84 | 51 | 208 | 58 | 51 |
| 22 | 34 | 47 | 284 | — | — |
| 23a | 41 | 29 | 335 | 38 | 50 |
| 23b | 30 | — | 284 | 32 | 36 |
| 24 | 55 | 38 | 204 | 28 | 28 |
| 25a | 72 | 26 | 175 | 32 | 27 |
| 25b | 78 | 60 | 162 | 28 | 33 |
| 26 | 114 | 84 | 218 | 68 | 46 |
| 27 | 32 | 64 | 194 | 74 | 91 |
| 28 | 122 | 23 | 462 | 66 | 41 |
| 29 | 69 | 45 | 178 | 39 | — |
| IV. Severely hypertensive | | | | | |
| 0 | 28 | — | 397 | 39 | 26 |
| 1a | 55 | — | 106 | 28 | 33 |
| 1b | 77 | 49 | 132 | 33 | 61 |
| 2 | 24 | 24 | 140 | 20 | 53 |
| 3 | 42 | — | 168 | — | — |

TABLE 2.—*Continued*

| Patient no. | Preload | | Load | Postload | |
|---|---|---|---|---|---|
| | 6 p.m. to 6 a.m. (ml./hr.) | 6 a.m. to 9 a.m. (ml./hr.) | 9 a.m. to 12 noon (ml./hr.) | 12 noon to 6 p.m. (ml./hr.) | 6 p.m. to 6 a.m. (ml./hr. |
| V. Labile hypertensive | | | | | |
| 34 | 31 | 149 | 113 | 46 | 35 |
| 35 | 45 | 52 | 203 | 43 | 58 |
| 36 | 34 | 15 | 149 | 15 | 20 |
| 37 | 85 | 66 | 130 | 57 | 42 |
| 38 | 30 | 7 | 56 | 50 | 25 |
| 39 | 72 | 31 | 125 | 48 | 27 |
| 40 | 32 | 43 | 110 | 48 | 25 |
| 41 | 37 | 42 | 298 | 40 | 19 |
| VI. Hyperadrenocorticism | | | | | |
| 42 (pre) | 38 | 35 | 162 | 76 | 85 |
| 42 (post) | 30 | 44 | 81 | 56 | 82 |
| 43 | 106 | 9 | 284 | 56 | 63 |

the assumption that all excreted sodium was derived from the infused load and err in indicating a higher percentage output than if basal excretion were subtracted. An increase in total body sodium in this period occurred only in the normotensive and mildly hypertensive groups. Nevertheless these subjects with excess body sodium excreted less in the last postload period.

Urine volume followed a pattern similar to sodium, mean values running so parallel as to suggest an interrelationship (tables 2 and 3). Under load, the normotensive subjects excreted 99.0 ml. per hour compared to 175, 244, and 206 ml. per hour respectively in the first 3 hypertensive groups. Water intake in the postload periods was not directly supervised. The data reveal no statistically significant differences between groups. The rate of urine excretion, like the rate of sodium excretion, was generally less in the postload than in the preload overnight period. Urine volume during load correlated with blood pressure in a similar manner as did the excretion of sodium. An inverse relationship was noted between urinary specific gravity during the load periods and the blood pressure (fig. 3). A similar correlation was not observed during the morning preload period. This relationship therefore was not caused by the hypertensive patients being less able to concentrate their urine. The blood pres-

TABLE 3.—*Mean Values of Sodium Excretion and Urine Volume*

| Blood pressure (mm. Hg) | Sodium Excretion: Preload 6 p.m. to 6 a.m. (mEq./hr.) | Preload 6 a.m. to 9 a.m. (mEq./hr.) | Load 9 a.m. to 12 noon (mEq./hr.) | Postload 12 noon to 6 p.m. (mEq./hr.) | Postload 6 p.m. to 6 a.m. (mEq./hr.) | Excretion of Infused Load: In 3 hrs. (%) | In 21 hrs. (%) | Urine Volume: Preload 6 p.m. to 6 a.m. (ml./hr.) | Preload 6 a.m. to 9 a.m. (ml./hr.) | Load 9 a.m. to 12 noon (ml./hr.) | Postload 12 noon to 6 p.m. (ml./hr.) | Postload 6 p.m. to 6 a.m. (ml./hr.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I. Normotensive (10) | | | | | | | | | | | | |
| 108/67 | 6.2 | 3.5 | 14.5 | 7.9 | 5.1 | 20 | 75 | 55.6 | 21.3 | 99 | 44.7 | 49.8 |
| II. Mildly hypertensive (8) | | | | | | | | | | | | |
| 155/100 | 6.5 | 3.8 | 20.7 | 6.8 | 4.2 | 29 | 67 | 51.1 | 30.6 | 175 | 38.4 | 33.6 |
| III. Moderately severely hypertensive (11) | | | | | | | | | | | | |
| 175/116 | 7.9 | 6.9 | 31.1 | 7.8 | 6.6 | 41 | 97 | 69.9 | 45.1 | 244 | 47.4 | 46.3 |
| IV. Severely hypertensive (4) | | | | | | | | | | | | |
| 214/136 | 7.2 | 5.2 | 45.6 | 6.8 | 7.8 | 66 | 133 | 40.0 | 37.0 | 206 | 29.8 | 42.0 |
| V. Labile hypertensive (8) | | | | | | | | | | | | |
| 124/72 | 7.8 | 9.3 | 25.4 | 10.7 | 5.6 | 34 | 91 | 45.8 | 50.6 | 148 | 43.3 | 31.4 |

When duplicate experiments were performed on the same patient, the average of the two is used for computing mean values.

Number of patients in each group indicated in parentheses.

sure did not correlate with potassium excretion or urine pH either after load or in the basal periods.

*Factors Affecting Reproducibility of the Test.* A series of repeated experiments on selected subjects was performed in which the effect was studied of spontaneous blood pressure fluctuations and of alterations in dietary sodium intake. These are detailed in figure 4. In the first 4 instances prior diets and mean blood pressures were comparable at the time of each test. Characteristic excretory responses to load were maintained although percentage changes from test to test were considerable. In another individual (no. 20, *a*, *b*) a spontaneous blood pressure decline was associated with a reduction in sodium output at rest and under load. Variations in dietary sodium in other patients (nos. 12, 21 and 25) did not produce any directional alteration in the excretory response to loading but instead, the changes in excretion of sodium in general varied in the same direction as mean blood pressure.

*Pattern of Sodium Excretion of Labile Hypertensive Individuals.* Table 3 reveals that labile hypertensive patients as a group show an excretory pattern for sodium and water similar to mildly hypertensive patients. Individual changes are presented in table 1 and figure 2. Some dependence of sodium excretion on blood pressure is suggested. If only the first 4 are selected (nos. 34–37) their mean blood pressure is 110/69 mm. Hg, which is almost identical with that of the normotensive subjects. Average sodium excretion values for the normal group and for these 4 labile hypertensive subjects were respectively: overnight, 6.2 and 8.0; load, 14.5 and 17.8 mEq. per hour. Those patients in the labile hypertensive group with the higher, but still normal blood pressures (particularly no. 41) contributed disproportionately to the high average sodium excretion for the group. These last 4 subjects had a mean blood pressure of 137/75 mm. Hg, an average overnight sodium excretion of 7.6 mEq. per hour, and a load excretion of 33.0 mEq. per hour.

It might be argued that severity of the labile hypertension was not properly estimated by the blood pressure reading at the time of testing. If those 4 patients with the higher previously reported blood pressures be selected (nos. 34, 37, 38, 40), their average overnight or load sodium excretion is actually less than that of the 4 patients with lower blood pressures.

*Sodium Excretion in Hypertensive Patients Having Increased Adrenocortical Function.*

Two individuals were studied who had adrenocortical hyperfunction.* S. T. (no. 42) was a patient with cyclic salt retention whose blood pressure was normal at the time of testing. At operation, adrenal cortical hypertrophy was found and one adrenal gland was removed together with three quarters of the other. Table 1 shows excretion rates prior to and after adrenalectomy. The postoperative sodium excretion rate in response to loading is not so great as it was preoperatively. Patient R. G. (no. 43), had an adrenocortical carcinoma and a blood pressure that averaged 168/123 mm. Hg. There was a high sodium excretory rate in the load period. During the last postload period (6 p.m. to 6 a.m.), the excretory rates of these 2 patients approached those of normal and hypertensive patients.

## Discussion

These observations together with those cited[1-9] leave no doubt concerning the tendency of hypertensive patients to excrete an excessive proportion of infused sodium and water. This abnormality is made evident by measuring the 3-hour sodium, chloride, or water excretion following a hypertonic sodium chloride load. The defect can also be demonstrated after mannitol loading[6] and hypertensive patients show an increased rate of diuresis even after water loading.[8] Green and co-workers[5] found in some of their hypertensive patients an increased basal excretion of sodium, chloride, and water. Our studies show a tendency in this direction. It was not observed by Birchall et al.,[9] nor by Renwick, Robson, and Stewart,[10] who controlled sodium intake. If these hypertensive patients are in salt balance then a sodium output that is increased by 1.5 mEq. per hour would require the intake of 830 mg. sodium per day in excess of that ingested by the normotensive subjects. Such an increase in salt intake could either cause the excretory abnormality or be its consequence. The latter appears more reasonable since short periods of dietary sodium restriction in our studies did not alter the responses to sodium chloride loading; the defect applies to water excretion as well;[6, 8] salt excretion follows the blood pressure level in the same individual, and the abnormality has been shown to exist in animals with diverse forms of hypertension.[11, 12] However, it is not possible to exclude entirely the contrary argument that increased salt appetite precedes and causes hypertension and determines the excretory pattern.[13] The previously mentioned observations on the labile hypertensive group are of interest, since these patients may represent an early form of the disease. Although variation between individuals was large, their salt excretion and presumably their sodium intake were slightly above normal at rest.

If the excretory abnormality is a consequence of hypertension, one could postulate that the hypertensive patient either imposes a greater salt and water load on the tubular transfer mechanism or rejects more of the load. So far as an increased tubular load is concerned, in a previous study hypertensive patients did not show an increased glomerular filtration rate following salt loading and indeed, when compared with normotensive patients, some even had measurable reductions in glomerular filtration rate.[1] The possibility that the tubular sodium load is increased by elevations in serum sodium must also be considered. Although the previous study of venous blood showed no increase in sodium concentration except in the mildly hypertensive group,[1] others have reported slightly elevated plasma sodium levels in hypertensive patients[8, 14-16] and Johnson and co-workers[17] have shown an elevated sodium in the spinal fluid. It is possible that the arterial plasma sodium of hypertensive patients after load might be increased to a greater extent than that of normotensive individuals if sodium content were elevated in the arterial wall[18] or the extracellular space.[19, 20] Hyperexcretion of sodium then would reflect excess body sodium. However, total exchangeable

*We are indebted to Drs. Jerome Conn and David Streeten, and the members of the Division of Endocrinology and Metabolism, for the opportunity to study these patients.

body sodium was not increased in all of Ross's hypertensive patients.[19]

On the other hand, if the filtered load of sodium is not elevated then there must be a greater rejection of sodium, chloride, and water by the renal tubule in hypertension. This would be consistent with the view that a tubular transport mechanism is the first to suffer in this disease.[21, 22] However, a diminished rate of transfer of filtrate through the tubular wall with consequent increase in urine flow may be secondary to the hypertension as indicated by Shipley and Study.[23] Polyuria has been observed at the onset of hypertension in a case of unilateral renal disease.[24] This might be due to a similar mechanism.

If increased tubular rejection of sodium and water is the primary abnormality causing the increased excretion of sodium chloride loads in hypertensive subjects, it may be the result of either neurogenic or humoral influences or of a local defect. The patients described by Thompson et al. showed a proportionately greater decrease in the excretion of infused sodium and water than reduction in blood pressure immediately after a presumably complete sympathetic renal denervation. However, since some reduction in blood pressure also occurred, it is not possible from these studies to evaluate the precise role of the nervous system alone in causing an augmented sodium chloride excretion in hypertension.[7]

Among possible humoral influences, the secretion of the adrenal cortex, the adrenal medulla, and the pituitary, as well as renin, deserve consideration. Hypertensive patients are said to excrete excess aldosterone in the urine.[25] Furthermore, patients with hyperadrenocorticism excrete excessive amounts of sodium and water after loading.[9, 26] However, London and Terry[27] noted a negative Soffer test in essential hypertension. It does not appear likely that the abnormality under consideration is due to increased secretion of salt-retaining steroid from the adrenal cortex.

Norepinephrine infusion creates an increased peripheral vascular resistance similar to that seen in essential hypertension. However, the excretion of sodium and potassium is decreased and that of water unchanged or increased when this substance is infused into normotensive subjects.[28] It is therefore doubtful that this agent is involved in the excretory abnormality of sodium chloride.

With respect to pituitary influences, Heinbecker[29] suggested that in hypertension there is a depression of the secretion of the neural hypophysis. However, Birchall et al., applying the salt load test for diabetes insipidus devised by Hickey and Hare,[30] excluded altered antidiuretic hormone secretion on the basis that water excretion did not follow the pattern seen in that disease.[9] Sapirstein[31, 32] has suggested that the prime defect lies in avidity of the hypertensive subject's tissues for sodium, since hypertonic saline loading in hypertensive rats leads to a greater urinary excretion of water than of sodium. Similarly our own studies suggest a greater loss of water than of urinary solutes so far as can be judged from the greater decline in specific gravity of the urine of the hypertensive subjects after loading.

It is possibly significant that renin, or its reaction product, "angiotensin," causes water and sodium chloride diuresis without altering glomerular filtration rate. These effects have been reviewed by Smith[33] and Deming.[24] Hypertension resulting from bilateral renal artery clamping in the dog was shown by Stamler, Hwang, and Kuramoto[34] to be followed by a normal tubular rejection of sodium. Measurements of intrarenal vascular pressure were not performed.

There is an important body of evidence concerning the direct effect on electrolyte excretion of raising or lowering the renal arterial pressure of the isolated kidney. Richards and Plant[35] were the first to demonstrate that an increase in renal perfusion pressure increased excretion of the chloride ion and the rate of urine formation. Later, Selkurt[36] examined the perfused kidney and demonstrated that, with a rise in pressure, sodium

excretion rose more rapidly than glomerular filtration rate. Shipley and Study[23] also investigated the isolated kidney and found that an increase in perfusion pressure augmented urine flow. According to their theories this greater amount of excreted sodium could be attributed to increases in filtered load that are too small to measure, or to increased tubular rejection as a result of a rise in renal interstitial pressure. Regardless of the precise mechanism involved it seems most likely that an increased pressure in the renal vascular bed best explains the augmented sodium excretion that has been described in such a wide variety of hypertensive states. The effect on sodium excretion of fluctuations in blood pressure in the same subject and the good correlation of renal resistance with sodium excretion[1] can be more readily explained by assuming a direct relationship between perfusion pressure within the renal arterial vasculature and tubular sodium and water rejection than by some extrarenal influence.


## Summary

The hourly rate of sodium and water excretion over a 36-hour period before, during, and after intravenous administration of 2.5 per cent sodium chloride is described for 10 normotensive, 8 labile hypertensive, and 23 hypertensive subjects.

Average sodium excretion prior to load was slightly increased in the hypertensive patients but there was a considerable individual overlap with normotensive subjects. The hypertensive patients showed a greater sodium and water elimination immediately after load, but in subsequent periods the various groups resembled each other.

The response to sodium chloride loading was reasonably consistent on repeated determinations in the same individual, but varied in the direction of the blood pressure at the time of testing. No directional change was noted in the excretory response to load before and after a period of several weeks on a 200-mg. sodium diet.

Patients with labile hypertension in a normotensive phase showed very slight increases in sodium and water excretion after loading when compared to normal subjects.

Two patients with increased adrenocortical function showed an increased sodium and water elimination immediately after loading that resembled the excretory pattern of the hypertensive subjects.

The cause of hyperexcretion of sodium chloride and water loads by hypertensive subjects is discussed. The most likely explanation appears to be that a rise in pressure within the renal vessels acts directly to augment the tubular rejection of sodium chloride and water.

## Summario in Interlingua

Le mesura horari del excretion de natrium e de aqua in le curso de un periodo de 36 horas ante, durante, e post le administration intravenose de chloruro de natrium de 2,5 pro cento es describite pro 41 subjectos, i.e. 10 normotensive, 8 hypertensive labile, e 23 hypertensive.

Le excretion medie de natrium ante le cargation esseva levemente augmentate in le gruppo del hypertensivos, sed le valores individual monstrava un coincidentia considerabile con illos in le gruppo del normotensivos. Immediatemente post le cargation, le patientes hypertensive monstrava un plus grande excretion de natrium e de aqua, sed in periodos subsequente le varie gruppos se resimilava.

Le responsa al cargation con chloruro de natrium remaneva satis uniforme in repetite determinationes in le mesme individuo sed variava in le direction del pression de sanguine al tempore del test. Nulle alteration directional esseva notate in le responsa excretori al cargation con sal ante e post un periodo de plure septimanas de un dieta con 200 mg de natrium.

Patientes con hypertension labile qui se trovava in un phase de normotension monstrava levissime augmentos del excretion de natrium e de aqua post cargation, comparate con subjectos normal.

Duo patientes con augmento del function adrenocortical monstrava un augmentate excretion de natrium e de aqua immediatemente

post le cargation. Lor comportamento excretori resimilava illo de subjectos hypertensive.

Le causa del hyperexcretion de chloruro de natrium e de aqua per subjectos hypertensive es discutite. Le explication le plus plausibile es probabilemente que un augmento del pression intra le vasos renal effectua directemente un augmentate rejection de chloruro de natrium e de aqua per le tubulos.

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# Medical Eponyms

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**Malpighian Corpuscles.** "The Internal Glands of the Kidneys and their Connection with the Blood Vessels" (*De internis glandulis renalibus, earumq: continuatione cum vasis*) is the title of the section of his discussion of the kidneys in which Marcello Malpighi (1628-1694), Primarius in the Academy of Medicine at Messina, describes these structures. The quotation is taken from the edition of his "Anatomical Essay on the Structure of the Viscera" (*De Viscerum Structura Exercitatio Anatomica*) published at London in 1669, chapter III, page 85. The first edition was published at Bonn in 1666.

"Since we have shown in a previous section that glands are found in the kidneys, and since, as will be shown below, these perform a special function in the excretion of the urine, for these reasons it is advisable to spend a little time on them. They are located in the outermost part of the kidneys, and are almost infinite in number, and, as I consider probable, correspond to the urinary vessels which join to make up the main bulk of the kidneys. They are gathered into separate bundles, more than forty in number, and it is by virtue of these that those small divisions arise which appear in all kidneys. Wherefore, as regards their shape, no definite description can be given on account of their minuteness and transparency, which is their chief characteristic: they seem, however, to be round like fish eggs, and while a black humor is passing through the arteries, they turn black; and you might say that all round them they have shoots, moving like twining tendrils, so that they appear to be wreathed around, so to speak—with this exception, however, that the main part which is fastened to the branch of the artery turns black while the rest retains its own color."

# Persistence of Fetal Ductus Function after Birth

## The Ductus Arteriosus as an Avenue of Escape

*By* HERBERT L. ABRAMS, M.D.

Within recent years there has been increasing interest in the presence of reversed flow through the ductus arteriosus. Most reported cases have been in older children and young adults. There is a group of cases in which the ductus serves as a site of a veno-arterial shunt in infancy, and thus continues to perform its fetal function. The conditions under which veno-arterial shunting persists after birth are illustrated and analyzed, and an effort is made to clarify the common features of these lesions.

THE function of the ductus arteriosus in the fetal circulation as a carrier of blood from the pulmonary artery to the aorta has been carefully studied and well documented.[1-5] It is generally accepted that the resistance to flow through the unexpanded lungs and fetal pulmonary arteries is sufficiently high to explain the passage of blood from the pulmonary artery into the descending aorta, which must constitute a receptacle of lower resistance. Some veno-arterial shunting through the ductus arteriosus may persist in a significant percentage of normal infants up to the age of 3 days,[6] although an arteriovenous shunt develops in most normal infants shortly after birth.[7] The pulmonary hypertension of the fetus is sustained for a variable time after birth.[7] Anatomic closure of the ductus normally occurs in 4 to 8 weeks after birth.[1, 8, 9] If the ductus remains patent, it usually functions as an arteriovenous fistula, aortic blood entering the relatively low resistance pulmonary circuit through the ductus.

Within recent years, there has been increasing interest in the association of pulmonary hypertension with patent ductus arteriosus, and in particular in the so-called "reversal of flow" that is occasionally found.* In such cases, the ductus arteriosus may constitute an "avenue of escape," which protects the right ventricle from having to force its entire output through a contracted pulmonary arterial bed, and thereby prevents it from failing.

The role of the ductus arteriosus as an escape valve may be discerned in a number of malformations. In all these conditions, the pulmonary vascular resistance must be higher than the resistance to blood flow in the descending aorta; but, in some, the fundamental difficulty almost certainly lies in the inability of pulmonary blood to reach the left heart and systemic circulation through normal channels (table 1). A description of the sites of obstruction to flow in these anomalies may clarify the role of the ductus when it retains its fetal function.

TABLE 1.—*Conditions Associated with Veno-Arterial Shunting of Blood Through the Ductus Arteriosus in Infancy*

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|---|
| 1. Isolated patent ductus arteriosus with marked increase in pulmonary resistance |
| 2. Patent ductus arteriosus associated with congenital pulmonary disease |
| 3. Pulmonary vein atresia |
| 4. Mitral atresia |
| 5. Mitral stenosis |
| 6. Aortic atresia |
| 7. Interruption of the aortic arch |
| 8. Preductal coaretation |

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*The term "reversal of flow" refers to a predominantly veno-arterial (pulmonary artery to aorta) shunt through the ductus arteriosus, in contrast to the arteriovenous (aorta to pulmonary artery) shunt that is usually present when the ductus arteriosus remains patent beyond the newborn period.

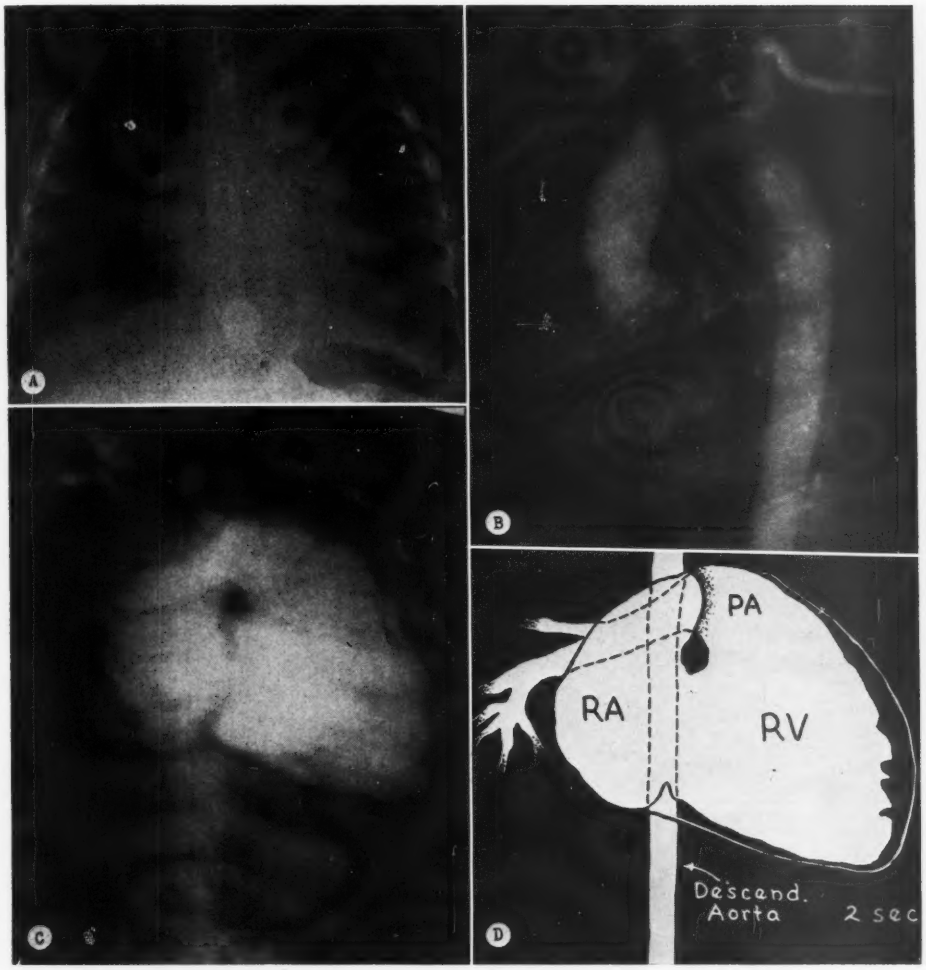


FIG. 1. *Case 1.* Isolated patent ductus with reversal of flow. *A.* Posteroanterior film. There is gross cardiac enlargement, mainly right ventricular and right atrial as determined in the oblique projections. Peripheral vascularity is diminished, and the central vessels are poorly delineated. The diminished vascularity is a reflection of increased resistance in the pulmonary arterial bed. *B.* Retrograde brachial aortogram. The opaque medium has been injected into the brachial artery, and fills the left subclavian artery, the aortic arch and the descending thoracic aorta. Minimal reflux into the mouth of the ductus arteriosus is visible (*arrow*). *C.* and *D.* Angiocardiogram demonstrates the enormous size of the right ventricle (*RV*) and its outflow tract. The main pulmonary artery (*PA*) is also enlarged. There is an abrupt taper in the size of the pulmonary arteries beyond the main branch division. Synchronous with pulmonary artery opacification, the descending thoracic aorta opacified through the ductus arteriosus. At autopsy, the only congenital cardiac anomaly was a large patent ductus arteriosus. (*RA* = right atrium.)

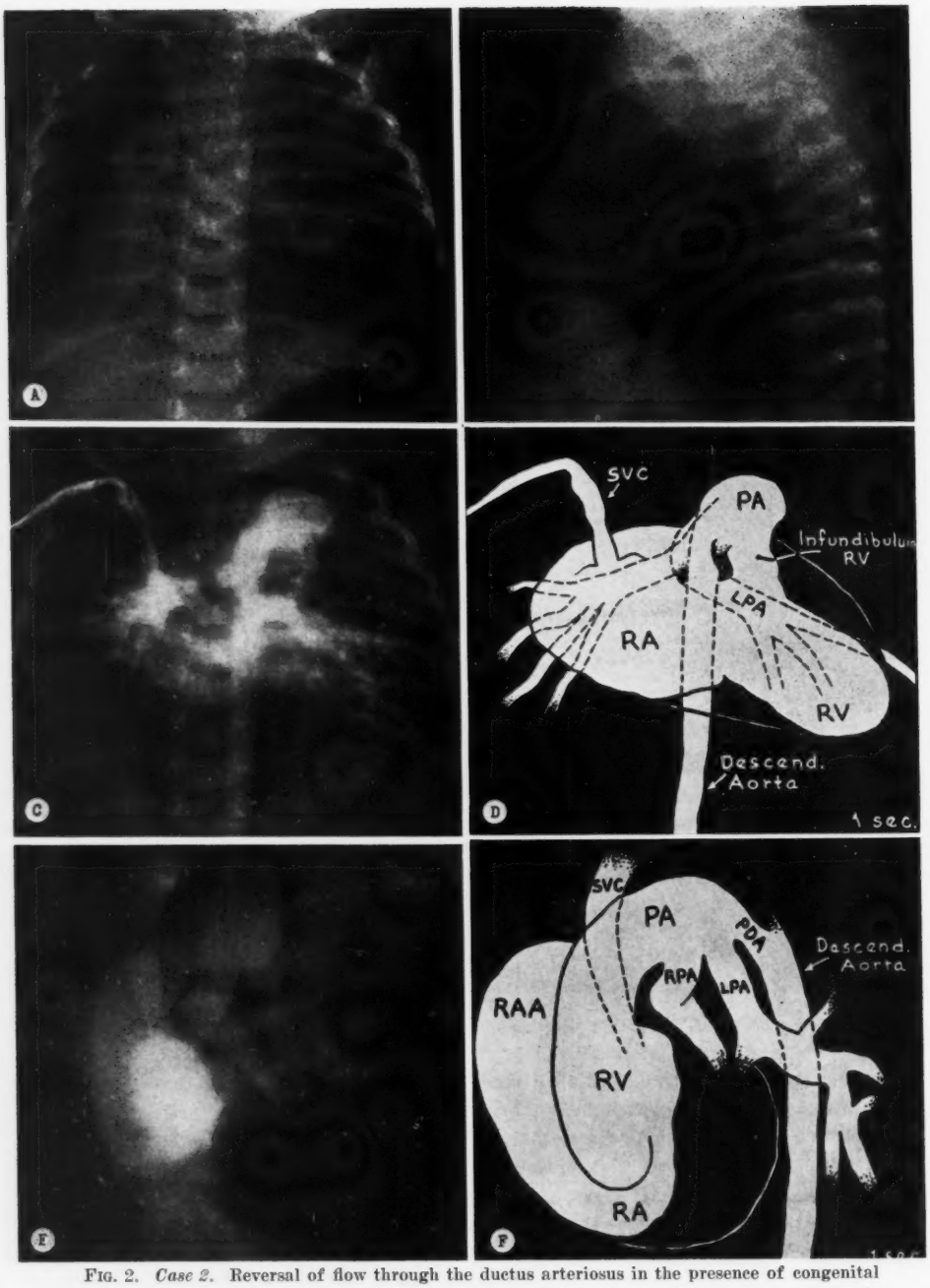


FIG. 2. *Case 2.* Reversal of flow through the ductus arteriosus in the presence of congenital pulmonary disease. *A.* Posteroanterior projection. The cardiac outline cannot be clearly delineated, indicating the presence of disease anteriorly placed in the lungs. Hyperexpansion of the lungs is noted. *B.* Left lateral projection demonstrates the overexpanded lower lobes,

*(Continued on opposite page)*

## Sites of Increased Resistance to Blood Flow when the Ductus Arteriosus Retains Its Fetal Function

### . *In the Pulmonary Arterial Bed (Isolated Patent Ductus Arteriosus with Reversal of Flow)*

*Case 1.* This infant was noted to have tachypnea shortly after birth, and clubbing of the toes, associated with lower limb cyanosis, by 9 months. He was underdeveloped, and gradually developed intractable right heart failure, with generalized cyanosis. On physical examination a right ventricular heave, a soft systolic murmur to the left of the sternum, and a loud pulmonic second sound were noted. The red blood cell count was 8.7 million mm.$^3$ and the hemoglobin 16 Gm. per 100 ml. The electrocardiogram showed a pattern of right ventricular hypertrophy.

Roentgenologic studies showed cardiac enlargement, mainly right ventricular, with a striking diminution in peripheral vascularity (fig. 1*A*). The clarity of the peripheral lung fields indicated diminished blood flow through the pulmonary arterial bed, reflecting the increased pulmonary resistance. A retrograde aortogram (fig. 1*B*) demonstrated no evidence of coarctation, and angiocardiographic studies (fig. 1*C*) showed opacification of the descending aorta from the pulmonary artery through a patent ductus arteriosus. In spite of therapy, intractable right heart developed, and death followed. At autopsy, a patent ductus arteriosus was the only cardiovascular malformation found. Marked right ventricular hypertrophy was present.

*Comment.* A number of recent studies have clarified the clinical, radiologic, and physiologic criteria for diagnosis of patent ductus arteriosus with reversal of flow.[10–17] There has been much speculation as to whether the increase in pulmonary resistance develops because of a sustained elevation of pulmonary blood flow, or is congenital in origin. Almost certainly, both explanations are correct. In case 1, as in other cases with cyanosis at birth and thereafter,[16] the veno-arterial shunt of the fetus was present during the postnatal period and hence pulmonary resistance must have been sustained at the fetal level. In those cases in which the reversal of shunt and development of cyanosis later in life has been verified, the pulmonary resistance must have increased over a period of years. This is in accord with experimental evidence indicating that marked pulmonary hypertension can be produced by creating an artificial "ductus arteriosus."[20] When the ductus is the site of a large right-to-left shunt in older patients, it is again fulfilling the function of an escape valve. Surgical closure is usually accompanied by right heart failure and death.[16, 18, 19]

### 2. *In the Pulmonary Parenchyma (Reversal of Flow Through the Ductus Arteriosus in the Presence of Congenital Pulmonary Disease)*

*Case 2.* A 5-week-old baby entered the hospital because of persistent respiratory distress. On physical examination tachypnea and tachycardia were apparent. There was a grade II systolic murmur heard best in the second left intercostal space, associated with a loud pulmonic second sound. Conventional roentgenologic studies demonstrated bilateral upper lobe collapse (or failure of expansion) with hyperexpansion of the lower lobes (fig. 2). On bronchography, no upper lobe bronchi could be delineated. The heart borders were difficult to define. Angiocardiography, performed in order to delineate the pulmonary arterial branches, demonstrated larger central pulmonary arteries with absence of both upper lobe pulmonary arteries and filling of the descending thoracic aorta from the pulmonary artery through a large ductus arteriosus (figs. 2*C*–2*F*). Retrograde thoracic aortography showed no evidence of coarctation of the aorta. The child is still alive but severely ill.

*Comment.* In the absence of necropsy

and the areas of density anteriorly placed which represent the unexpanded or collapsed upper lobes. No upper lobe bronchi were delineated on bronchography. *C.* and *D.* Angiocardiogram, anteroposterior projection. A huge pulmonary artery (*PA*) is opacified from the right ventricle (*RV*), and immediately thereafter, the descending thoracic aorta is clearly filled with the opaque medium. No upper lobe pulmonary arteries are visible, and there is truncation of the remaining pulmonary arteries. *E.* and *F.* Lateral angiocardiogram demonstrates the opaque medium entering the right atrium (*RA*) from the superior vena cava (*SVC*). Right ventricular (*RV*) and pulmonary artery (*PA*) opacification follow. Synchronous with this, the descending thoracic aorta is opacified through a patent ductus arteriosus (*PDA*).

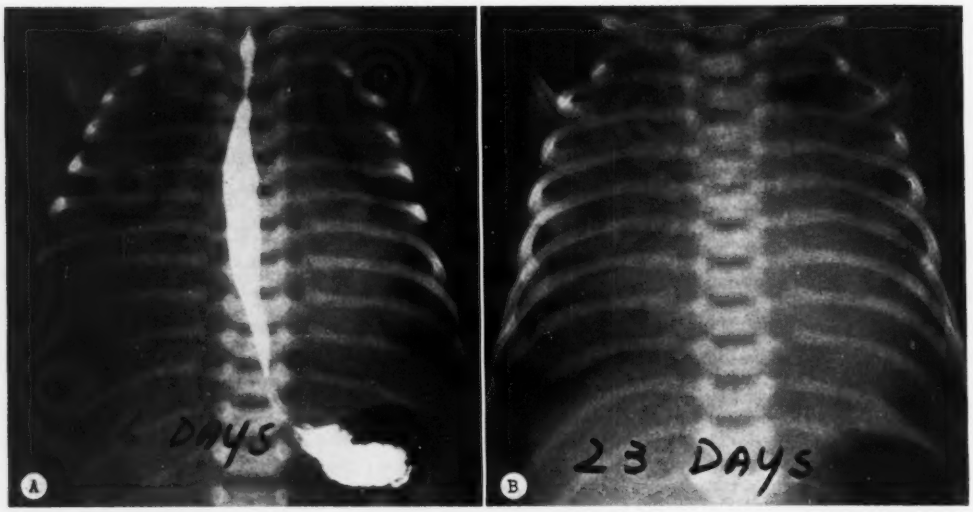


FIG. 3. *Case 3.* Reverse ductus flow in the presence of pulmonary vein atresia. *A.* Posteroanterior projection 16 days of age. There are marked bilateral pulmonary congestion and cardiac enlargement. The right heart border is obscured by the overlying pulmonary densities. *B.* Posteroanterior projection, 23 days of age. Both lungs are now diffusely opaque except at the periphery. The degree of pulmonary congestion has increased markedly during the preceding week. (Compare with figure 5*A*.)

proof, it is impossible entirely to exclude other factors that might be responsible for reversal of flow. On the other hand, it is well known that extensive pulmonary disease—such as fibrosis and emphysema—may increase the resistance to blood flow through the lungs and provoke pulmonary hypertension and cor pulmonale.[21] Agenesis of the upper lobes, associated with marked hyperexpansion of the lower lobes, offers a reasonable explanation for increased resistance to flow through the lungs. Whether hypoxia, which is known to cause elevation of pulmonary artery pressure,[22] is a major factor in the increased resistance, or whether compression of the pulmonary capillary bed and the smaller arterial branches is an important factor[23] cannot be stated with assurance.

Cardiac enlargement has been noted to accompany pulmonary disease in newborn infants.[23, 24] In these cases, the early cor pulmonale that is noted with neonatal atelectasis or extensive neonatal pneumonitis may be reversed with regression of the pulmonary disease.[25] The cor pulmonale itself reflects the increased resistance to blood flow through the lungs.[23] In this regard, it is of interest that a recent case has been reported in which agenesis of the left lung was associated with reversal of flow through the ductus arteriosus, although this patient was in a somewhat older age group.[26]

### 3. *In the Pulmonary Venous Bed (Atresia of the Pulmonary Veins)*

*Case 3.* A 16-day-old infant entered the hospital because of tachypnea and tachycardia that had developed at about the age of 1 week. Grade I systolic and diastolic murmurs were heard in the first and second left interspaces. Rales were audible at both bases, the liver was down 5 cm. below the costal margin, and there was suggestive cyanosis of the nailbeds. The electrocardiogram showed a pattern of right ventricular hypertrophy. Chest films showed diffuse mottling of both lungs with poorly defined heart borders but obvious cardiac enlargement (fig. 3*A*). It was impossible to be certain whether the pulmonary densities were all on the basis of pulmonary edema, or whether there was significant pulmonary parenchymal dis-

ase. In spite of oxygen therapy and continued igitalization, the infant's course progressively orsened. At 23 days of age, the mottling of the ungs had increased significantly (fig. 3*B*). Death ecurred at 1 month of age. At autopsy, the right trium and right ventricle were enormous, but the ft atrium and left ventricle were diminutive (fig. 3*C*). A common pulmonary vein with a completely occluded lumen was connected to the left atrium. The ductus arteriosus was patent, and there was a small patent foramen ovale. Marked pulmonary congestion and large bronchial and subpleural veins were noted.

*Comment.* Blood leaving the right ventricle entered the pulmonary arteries and veins, was unable to reach the left atrium through the occluded common pulmonary vein, and was forced to leave the pulmonary vascular bed through the ductus arteriosus or bronchial collateral veins. Because of the obstruction to venous return from the lungs, marked pulmonary congestion developed (clearly explaining the roentgen findings).

The fetal circulation was not sufficiently embarrassed to cause death *in utero* because right heart blood could reach the left heart through the patent foramen ovale, and could reach the aorta through the ductus arteriosus. The fact that survival to 30 days was possible is unusual, since blood exposed to alveolar oxygen could only leave the lungs through the bronchial veins, flowing into the azygos system, and returning to the heart through the superior vena cava. This permitted only a limited amount of mixing of systemic venous blood and oxygenated pulmonary venous blood in the right cardiac chambers. Blood from the right heart reached the systemic circulation through the ductus arteriosus or possibly through the small patent foramen ovale. The marked hypoplasia of the left atrium and left ventricle reflects the insignificant role that they played in the circulation.

Edwards et al.[27] have described a case of atresia of a common pulmonary vein, but the presence of a communication between the proximal portion of the vein and the superior vena cava enabled pulmonary venous blood to leave the lungs without excessive pulmonary engorgement. Their case, then, is essentially one of total anomalous pulmonary venous return into the superior vena cava. In such cases, one might expect the ductus arteriosus to remain open; but the tremendous dilatation of the right atrium is usually accompanied by a large patent foramen ovale, allowing right-to-left shunt. Nonetheless, in a few such cases, patency of the ductus has persisted.[28, 29] Similarly, in the rare cor triatriatum, patency of the ductus arteriosus might be expected, but has not yet been reported.[30]

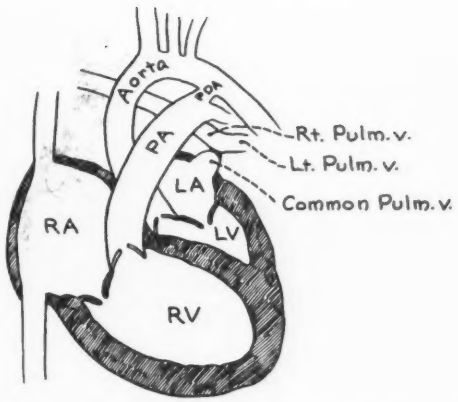


FIG. 3 *C*. Diagrammatic representation of the necropsy findings. The right atrium (*RA*) and right ventricle (*RV*) were grossly enlarged, and the left atrium (*LA*) and left ventricle (*LV*) hypoplastic. The ductus arteriosus (*PDA*) was widely patent and communicated with the descending thoracic aorta. There was atresia of the common pulmonary vein. Examination of the lungs demonstrated large bronchial and subpleural veins, in addition to marked pulmonary congestion and edema.

4. *At the Mitral Valve*

*Mitral Atresia with Patent Foramen Ovale*

*Case 4.* A Negro infant was noted to be cyanotic on the second day of life. Respirations became labored on the following day. On physical examination, a systolic murmur was heard over the precordium and a large liver was felt. The electrocardiogram showed a pattern of right ventricular hypertrophy. Chest films demonstrated gross cardiac enlargement, mainly involving the right cardiac chambers, and moderate pulmonary engorgement (fig. 4*A*). In spite of digitalization, the child died 4 days later. Autopsy demonstrated mitral atresia, a huge pulmonary artery, and a patent ductus arteriosus larger than the proximal

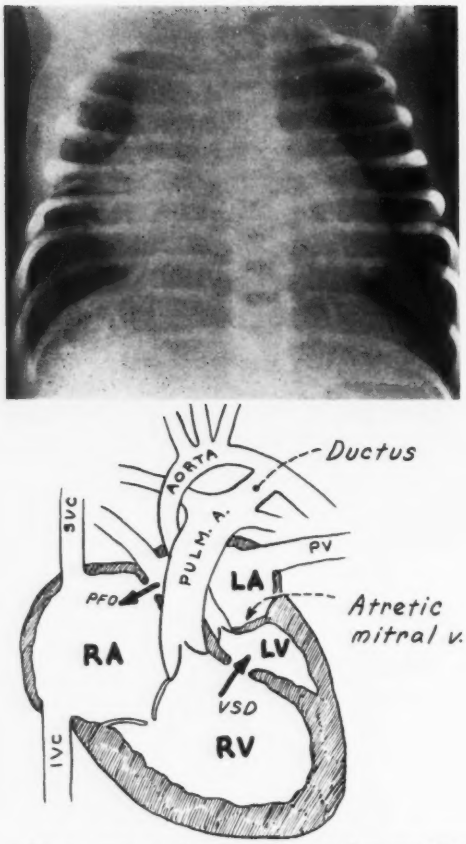


FIG. 4. *Case 4.* Reversal of ductus flow associated with mitral atresia and a patent foramen ovale. *Top.* Posteroanterior projection. There are gross cardiac enlargement, a large right atrial silhouette, and some elevation of the cardiac apex. Pulmonary engorgement is visible. *Bottom.* Diagrammatic representation of the circulation as found at autopsy. The right atrium (*RA*) and right ventricle (*RV*) were huge, and the left atrium (*LA*) and left ventricle (*LV*) diminutive. The mitral valve was atretic. A patent foramen ovale (*PFO*) was present. A patent ductus arteriosus larger than the aorta allowed flow from the pulmonary artery into the descending aorta. In addition, a ventricular septal defect (*VSD*) was present.

aorta (fig. 4*B*). A ventricular septal defect, large right cardiac chambers and a hypoplastic left atrium, left ventricle, and aorta were found. The foramen ovale was patent.

*Mitral Atresia with Imperforate Foramen Ovale*

*Case 5.* A full-term baby was noted to be cyanotic and tachypneic at birth. On physical examination no murmurs were heard. Respirations were rapid and shallow, and in spite of oxygen therapy cyanosis persisted and episodes of apnea were noted. Chest x-rays showed diffuse densities throughout both lung fields (fig. 5*A*). The child died 11 hours after birth, when she failed to be revived from an episode of apnea. At autopsy, mitral atresia with an imperforate foramen ovale, a single ventricle, a large ductus that supplied the entire systemic circulation, moderate coarctation, and aortic atresia were noted. (fig. 5*B*). Multiple collateral pleural vessels were present, and there was a good deal of fluid in the alveoli.

*Comment.* In the presence of mitral atresia, normal left atrial emptying into the left ventricle is obviously impossible. Blood can leave the left atrium only through a patent foramen ovale or an atrial septal defect.[31] If the foramen ovale is imperforate, the left atrium represents a blind alley, and right ventricular blood can only reach the systemic arterial circulation through a patent ductus arteriosus or by entering the left ventricle and aorta through a ventricular septal defect. Pulmonary venous blood returns to the right heart through bronchial collateral veins.

During fetal life, the major channel of blood flow to the systemic circulation in these cases is the ductus arteriosus. It is thus not surprising that the ductus persists after birth as a vessel of large size—frequently larger than the aorta—in many cases of mitral atresia. In virtually all cases in which the foramen ovale has been closed, the ductus arteriosus has been open.[32] But the difficulties confronting the cardiovascular system when mitral atresia is accompanied by an imperforate foramen ovale are too profound to support life for a significant period of time.

In case 4, it is interesting to speculate as to what the consequences of surgically producing a mitral valve orifice might have been. If this were feasible, all of the other lesions would have been readily amenable to open heart surgery, and the infant might then have ended up with isolated mitral insufficiency. As more of these cases are seen, the need to create experimental mitral insufficiency and to evaluate the critical degree of insufficiency becomes more important.

*Mitral Stenosis*

Although congenital mitral stenosis is

elatively rare lesion, a number of cases have een reported in which reversal of flow hrough the ductus arteriosus has been a com- licating factor.[33, 34] In one case reported ecently,[34] the angiocardiogram showed clear- y the continuity of the ductus arteriosus and he descending aorta. When a retrograde ortogram performed by injection into the ight brachial artery failed to show the aortic rch, the 11-month-old infant was explored n the assumption that he had coarctation of he aorta. Ligation of the ductus arteriosus was followed immediately by cardiac arrest and death. At autopsy, significant stenosis of the mitral valve and dilatation of the left atrium were found. The left ventricle and aorta were hypoplastic.

Because of the increased resistance to flow at the mitral valve, even during fetal life the ductus was probably utilized as a more important channel of flow into the systemic circulation than the foramen ovale. At birth, the increased left atrial and pulmonary venous pressure presumably helped to sustain the fetal pulmonary hypertension, or to produce pulmonary hypertension as may occur in adults with acquired mitral stenosis. The pulmonary vascular resistance must have been high to sustain the ductal right-to-left shunt that was present in fetal life.

### 5. *At the Aortic Valve (Aortic Atresia)*

*Case 6.* A female infant developed tachypnea, poor feeding, and cyanosis during the first week of life. A murmur was heard at 1 month of age. Admitted at the age of 6 months, she showed general cyanosis. Blood pressure by the flush method was 70 in the right arm and 100 in the right leg. The heart was enlarged, with rapid rate, a gallop at the apex, and a grade III systolic murmur maximal at the apex. The pulmonic second sound was loud. The liver was felt 2 fingerbreadths below the costal margin. The red blood cell count was 6.5 million per mm.$^3$ and the hematocrit 51 per cent. The electrocardiogram showed a pattern of right ventricular hypertrophy. Fluoroscopy and chest films demonstrated enlargement of the right atrium, right ventricle, and left atrium (figs. 6*A* and *B*). Peripheral pulmonary vascularity was diminished, and the central vessels were poorly seen. Arterial oxygen saturation in the right upper extremity was 47 per cent, and in the right lower extremity 46 per cent. Angiocardiography demonstrated opacification of the aorta from the pulmonary artery through a patent ductus arteriosus, with a site of coarctation proximal to the insertion of the ductus (fig. 6*C*–6*H*). The right atrium was enlarged, as was the left atrium, but the left ventricle was hypoplastic. Persistent opaci-

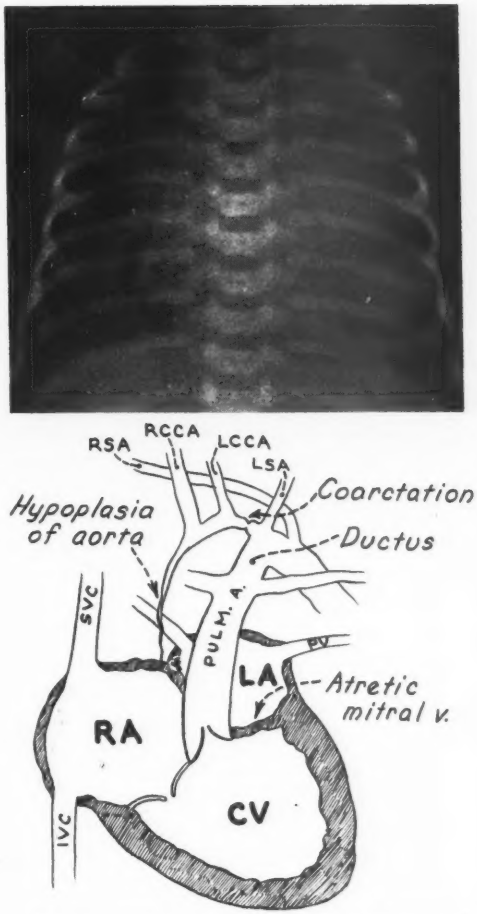


FIG. 5. *Case 5.* Reversed ductal flow associated with mitral atresia, imperforate foramen ovale and aortic atresia. *Top.* Posteroanterior projection. There are marked cardiac enlargement and gross pulmonary congestion. The lung fields resemble those in case 3 in which pulmonary vein atresia was present. *Bottom.* Diagrammatic representation of the autopsy findings. A large right atrium (*RA*) emptied into a common ventricle (*CV*), from which blood entered the pulmonary artery and through a large ductus arteriosus reached the aorta. Mitral atresia, an imperforate foramen ovale and aortic atresia were present, and there was a moderate degree of coaretation proximal to the ductus arteriosus. An aberrant right subclavian artery (*RSA*) was also noted.

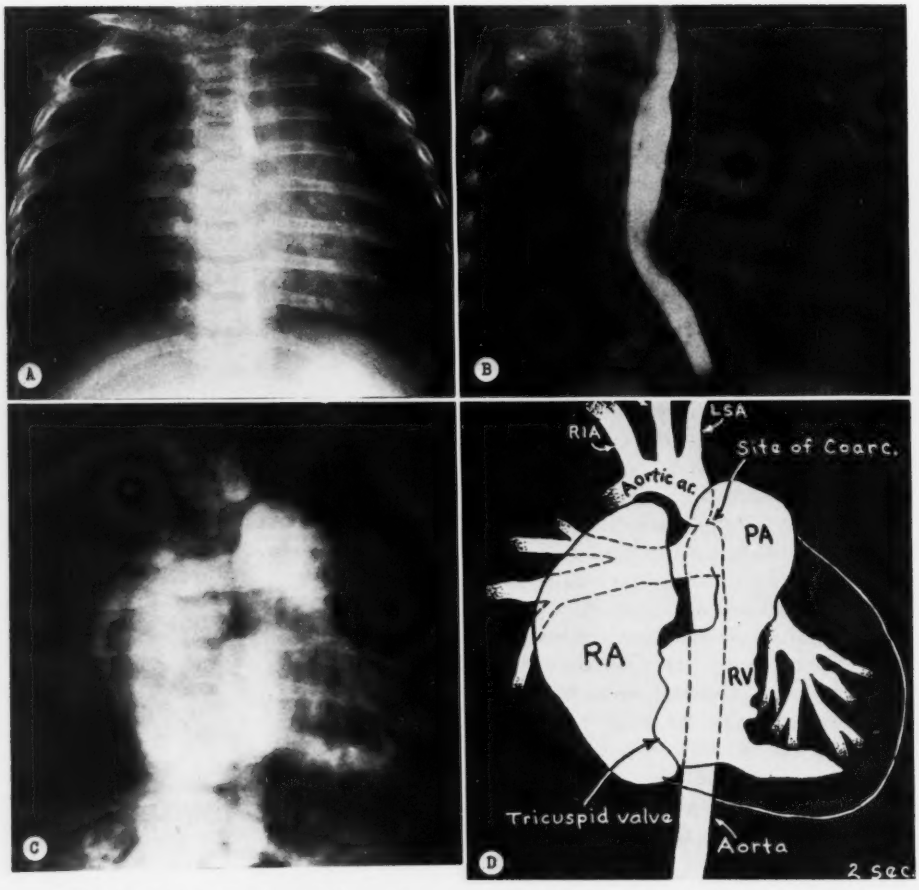


FIG. 6. *Case 6.* Reversal of ductus flow associated with aortic atresia. *A.* Posteroanterior roentgenogram. The heart is enlarged, with a prominent right atrial silhouette. Although the central vessels are moderately full, the peripheral vessels appear small. *B.* Right anterior oblique projection. There is definite left atrial enlargement as well as right ventricular enlargement. *C.* and *D.* Angiocardiogram, anteroposterior projection, 2 seconds. The descending thoracic aorta has filled from the pulmonary artery through the ductus arteriosus. The arch of the aorta is also opacified, but the ascending aorta is not visible.

fication of the right atrium suggested the presence of an atrial septal defect. The diagnosis of a large patent ductus arteriosus with reverse flow, hypoplasia of the left ventricle, mitral stenosis, coaretation of the aorta, and an atrial septal defect was made, and the child was considered inoperable, was digitalized, and sent home. She returned in serious condition at the age of 9 months and died 4 days after admission.

Autopsy showed aortic atresia, a hypoplastic left ventricle communicating only with the left atrium, a dilated left atrium, a large patent foramen ovale with an incompetent valve, and a huge right atrium and right ventricle. The main pulmonary artery was dilated and communicated with the descending aorta by way of a large ductus arteriosus (fig. 6*I*). Moderate stenosis of the mitral valve was apparent. Just proximal to the entrance of the ductus was a localized zone of coarctation. Marked intimal and medial thickening of the small and medium-sized pulmonary arteries was noted, and the pulmonary veins were dilated.

*Comment.* It seems apparent that the aortic atresia was the primary lesion in this case. During fetal life, the left cardiac chambers played no significant role and the heart functioned as a 2-chambered pump. All blood

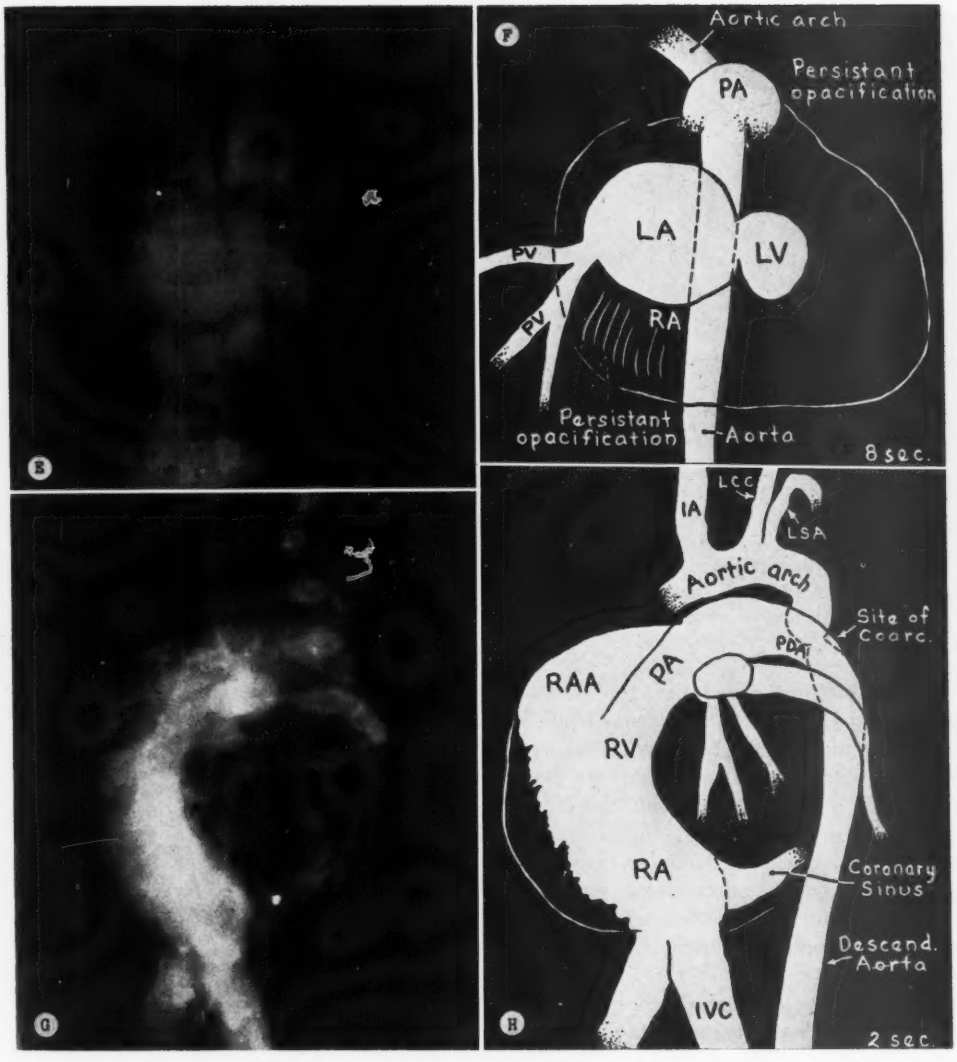


FIG. 6*E.* and *F.* The left atrium (*LA*) is now opacified and the pulmonary veins (*PV*) visible. A round sac is seen within the center of the cardiac silhouette, which represents the left ventricle (*LV*). There is persistent opacification of the right atrium, indicating a left to right interatrial shunt. *G.* and *H.* Steep right posterior oblique angiocardiogram, 2 seconds. The right atrium (*RA*), right ventricle (*RV*), and pulmonary artery (*PA*) are opacified, and the aorta has been filled through the ductus arteriosus (*PDA*). A site of narrowing adjacent to the ductus is visible in the aorta (*arrow*). Some coronary sinus reflux is also noted.

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e ductus arteriosus, the foramen ovale be-
g incapable of serving as a channel of right-to-left flow because of the aortic atresia. In the absence of a ventricular septal defect, the left ventricle became a functionless diverticulum. After birth, blood entering the left atrium from the lungs could only escape by way

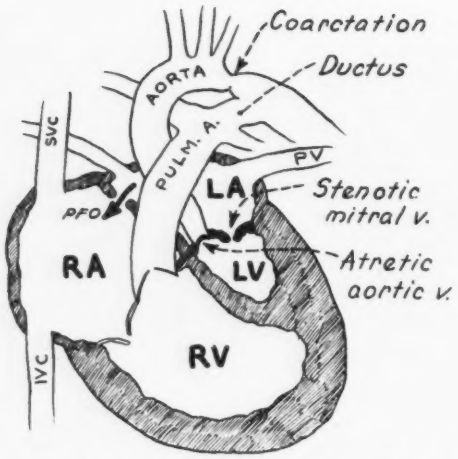


FIG. 6*I*. Diagrammatic representation of the autopsy findings. The right atrium (*RA*) and right ventricle (*RV*) are grossly enlarged, and the pulmonary artery (*PA*) is connected by a thick short ductus arteriosus to the descending aorta. A zone of coaretation is visible. The aortic valve is atretic, and moderate mitral stenosis is present. The foramen ovale (*PFO*) is patent.

of the foramen ovale and the right atrium. It then mixed with systemic venous blood in the right atrium and right ventricle, and entered the pulmonary artery either to reach the systemic circulation through the ductus or to be carried back through the pulmonary vascular bed. The remarkable aspect of this case is that survival to 9 months of age could occur with a functionally 3-chambered heart, aortic atresia, and moderate coaretation of the aorta that prevented even the mixed pulmonary artery blood from reaching the brain easily. Of further interest is the fact that the blood pressure of the upper extremity was lower than that of the lower extremity. This paradoxical finding was an effect of the coaretation, which, in the absence of aortic blood flow from the left ventricle, had precisely the opposite blood pressure effect from that usually observed in uncomplicated coaretation of the aorta.

Obstruction at the aortic valve must be of a high order if the fetal right-to-left shunt is to be sustained. In aortic atresia no blood can reach the ascending aorta from the left ventricle, and the ductus must remain patent if the systemic circulation is to receive any blood.[35–38] In congenital aortic stenosis, however, the left ventricle, which has an enormous reserve, is rarely faced with the kind of resistance that prevents the expulsion during ventricular systole of an adequate quantity of blood. The cardiac output in congenital aortic stenosis is usually normal at rest unless or until heart failure ensues.[39] It is of interest in this regard that we have not observed or noted in the literature any cases of congenital aortic stenosis complicated only by persistence of a right-to-left shunt through the ductus arteriosus.

### 6. *Beyond the Aortic Valve*

Although a number of anatomic variations in the site, length, and caliber of stenosis of the aortic arch or isthmus may be observed, cases of coaretation or interruption of the isthmus with reverse ductal flow should probably be considered as a group whose common denominator is the preductal location of the narrowed zone. If the narrowing is severe enough, and hence the obstruction to flow high grade, persistence of the fetal function of the ductus may occur. A number of such cases have been reported in the literature.[40–44] Because of the therapeutic implications of this lesion, it deserves careful study, and a few illustrative cases may serve to emphasize the dynamic aberrations, the importance of early diagnosis, and the possibilities of cure.

*Case 7*. This premature baby girl born at 7½ months cried only when stimulated vigorously. The respirations were shallow, and slight peripheral cyanosis was visible. The heart sounds were of good quality but the rate was somewhat slow. At 3 days of age there were cardiac enlargement, a gallop rhythm, and an apical systolic murmur. The radial pulses were readily felt, but no femoral pulsations were palpable. The liver was markedly enlarged. Electrocardiograms showed a pattern of right ventricular hypertrophy. Chest roentgenogram demonstrated cardiac enlargement, with pulmonary vascular engorgement (fig. 7*A*). On the ninth day of life, a loud systolic murmur was heard throughout systole, transmitted in all directions. On the following day the infant developed Cheyne-Stokes breathing and died. Autopsy demonstrated absence of the aortic arch with comple

nterruption of the isthmus of the aorta and a persistent large ductus (fig. 7*B*). The right ventricle was markedly hypertrophied. A ventricular eptal defect was present.

*Comment.* In this case, the combination of interruption of the aortic arch and reversal of flow through the ductus arteriosus was incompatible with life for more than a few days. That this is not always true is illustrated by the following case.

*Case 8.* An infant first seen at 4 months of age because of respiratory difficulty had been noted to have dyspnea first at 1 month of age, and cyanosis of the feet was observed at 2 months of age. Shortly before admission he had an episode of respiratory arrest. On physical examination blood pressure was 150/80 in the right arm and 90/70 in the legs. The heart was enlarged with a snapping second pulmonic sound and a faint systolic murmur along the left upper sternal border. The liver was felt 2½ fingers below the costal margin, and the femoral pulses were faintly palpable. The fingers were pink, the toes cyanotic. Red blood cell count was 6.1 million per mm.$^3$, hemoglobin 17 Gm. per 100 ml. Arterial oxygen saturation was 90 per cent in the right upper extremity, and 46 per cent in the right lower extremity. Electrocardiogram showed a pattern of right ventricular hypertrophy. Conventional radiologic studies showed moderate cardiac enlargement, mainly right atrial and right ventricular, and prominent central pulmonary arteries. Angiocardiogram showed a right-to-left flow through the ductus arteriosus, with opacification of the descending aorta from the pulmonary artery (fig. 8*A*). Retrograde thoracic aortogram showed complete interruption of the aortic arch (fig. 8*B*). This child is still alive at the age of 4½ years. His activity is limited and his physical signs are unchanged. Surgery has not been permitted.

*Comment.* In this patient, the right ventricle continues to supply all of the blood for the lower portion of the body through the ductus arteriosus, yet he has apparently reached a state of balance consistent with life. A final example of a somewhat more complicated case, which nonetheless fits in this category, deserves description.

*Case 9.* This 5-month-old girl entered the hospital because of heart failure, beginning at the age of 2 months and necessitating digitalization. She had had episodes of coughing and respiratory distress. On physical examination, tachypnea and irritability were noted. The heart was slightly enlarged and there was a systolic murmur over the

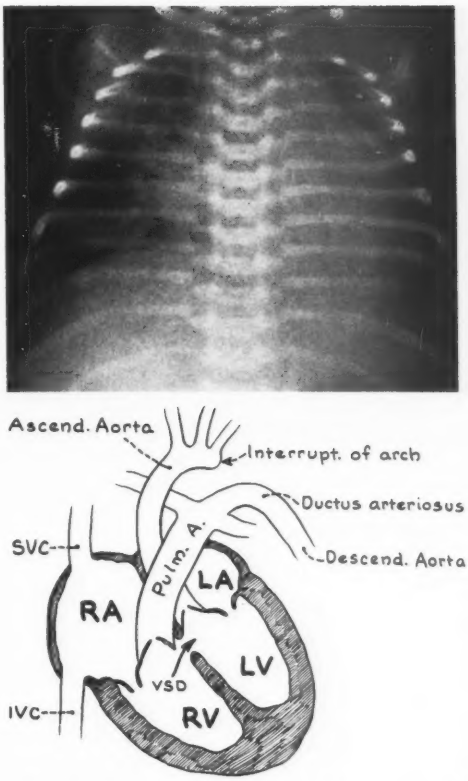


FIG. 7. *Case 7.* Reversed ductal flow associated with interruption of the aortic arch. *Top.* Posteroanterior film. The heart is grossly enlarged, and there is pulmonary congestion. The aorta cannot be delineated. *Bottom.* Diagrammatic representation of autopsy findings. There is complete interruption of the aortic arch. The pulmonary artery is continuous with the descending aorta through a patent ductus arteriosus. A small membranous ventricular septal defect (*VSD*) is present. (*RA* = right atrium, *RV* = right ventricle, *LA* = left atrium, *LV* = left ventricle.)

right second interspace. The second pulmonic sound was louder than the second sound at the aortic arch. The blood pressure was recorded as 90/60 in the arms and 115/70 in the legs by the cuff method. A right ventricular heave was noted. The lungs were clear. Hemoglobin was 12.2 Gm. per cent. The electrocardiogram was suggestive of biventricular hypertrophy. Radiologic studies demonstrated marked increase in cardiac size, with combined ventricular enlargement and increased pulmonary vascularity. Cardiac catheterization demonstrated a large left-to-right shunt

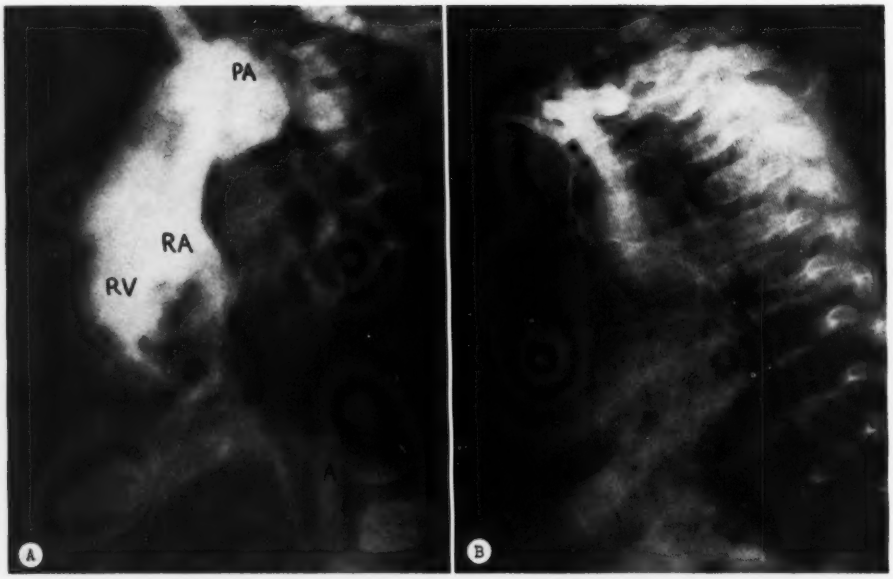


FIG. 8. *Case 8.* Reversed ductal flow associated with interruption of the aortic arch. *A.* Angiocardiogram in steep right posterior oblique projection. The opaque medium enters the right atrium (*RA*) through the superior vena cava, fills the right ventricle (*RV*) and the pulmonary artery (*PA*) and then opacifies the descending aorta (*A*) through the patent ductus arteriosus (*arrow*). *B.* Retrograde thoracic aortogram in steep right posterior oblique projection. Following injection of opaque medium into the right brachial artery, the innominate artery and ascending aorta are visualized, and there is obvious interruption of the aortic arch (*arrow*).

through a ventricular septal defect, and a right-to-left shunt through a patent ductus arteriosus. Arterial oxygen saturation was 93 per cent in the right upper extremity, and 80 per cent in the descending aorta. The pulmonary artery pressure was higher than the pressure in the descending aorta (table 2). Angiocardiogram demonstrated a right-to-left shunt through a patent ductus arteriosus with opacification of the descending aorta following pulmonary artery opacification, and a retrograde aortogram demonstrated complete stenosis of the aortic arch just beyond the origin of the left subclavian artery. Repair of the coaretation and surgical interruption of the ductus arteriosus were recommended.

TABLE 2.—*Catheterization Data on Case 9*

| | $O_2$ contents ml./100 ml. | | % Saturation | Pressures mm. Hg above midchest |
|---|---|---|---|---|
| Superior vena cava | 6.1 | 6.0 | 40 | |
| Inferior vena cava | 5.8 | | | |
| Right atrium | 6.2 | | 42 | 1 (mean) |
| Right ventricle | 11.5 | | 77 | 103/0 |
| Pulmonary artery | 11.5 | | 77 | 113/55 |
| Descending aorta | 11.9 | | 80 | 100/55 |
| Right hand capillary | 13.8 | | 93 | |
| Capacity | 14.9 | | | |

At surgery the narrowed segment of the aortic arch extended beyond the subclavian artery for about 2 cm., at which point a large ductus joined the distal aorta. The ductus was divided and the distal thoracic aorta mobilized and anastomosed to the proximal portion of the aortic arch. After a somewhat stormy postoperative course, the child on discharge, 2 weeks after surgery, was in relatively good shape. Closure of the ventricular septal defect is contemplated after a period of stabilization.

*Comment.* Although there was a right-to-left shunt through the ductus arteriosus in this child, surgical closure of the ductus and excision of the coarcted segment were possible and helpful. It must be stressed, however, that the pulmonary resistance need not have

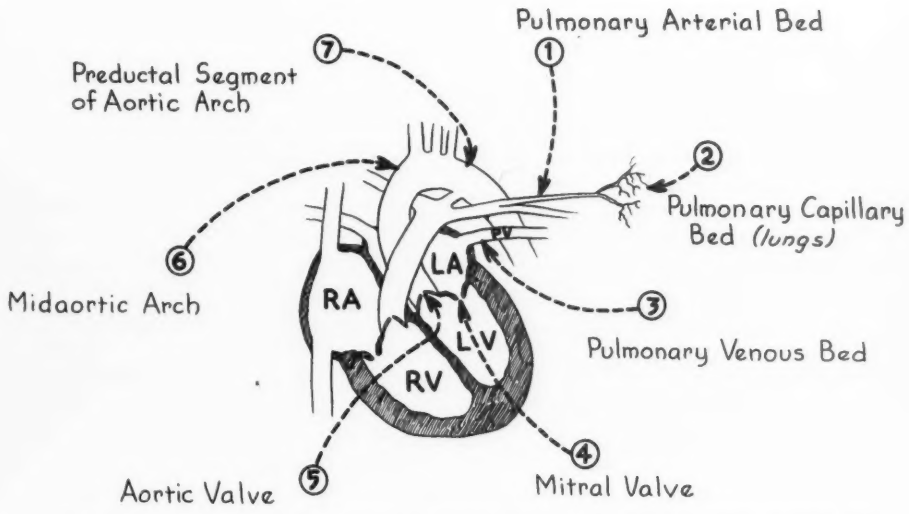


FIG. 9. Sites of increased resistance associated with veno-arterial shunting through the ductus arteriosus.

been significantly elevated in the presence of a large left-to-right shunt through the ventricular septal defect, in spite of the marked pulmonary hypertension.

## DISCUSSION

### 1. *Anatomic Basis of Persistent Fetal Ductus Function*

The common denominator of the malformations in which right-to-left flow through the ductus arteriosus persists after birth is the presence of a site of obstruction to blood flow in the pulmonary vessels, left heart, or aorta at some point beyond the pulmonary origin of the ductus arteriosus but proximal to its aortic insertion (fig. 9). In isolated patent ductus arteriosus with reversal of flow in infancy, the obstruction appears to be primary in the pulmonary arteriolar bed; in the presence of congenital lung disease and reversal of ductal flow, the pulmonary capillary bed may also be implicated in the production of increased resistance; the other sites of obstruction—the pulmonary veins, the mitral valve, the aortic valve, and the preductal portion of the aortic arch—are all more sharply defined.

A distinction must be made between the primary and the secondary site of increased resistance; for, no matter where the obstruction is, the pressure on the arterial side of the pulmonary vascular bed must be markedly elevated to support right-to-left ductal flow. If the pulmonary arterial change is primary in isolated right-to-left ductal flow in infancy, it seems reasonable to consider it secondary in such lesions as mitral or aortic atresia.

It has been pointed out that the thickened muscular pulmonary arteries of the fetus may persist in infancy and because of the small size of their lumens, produce a high resistance to blood flow through the lungs.[45, 46] Such vessels have been described in detail in patent ductus arteriosus with reversal of flow in the presence of preductal aortic coarctation.[40] What the precise stimulus is that prevents the thick muscular arteries from developing in the direction of the thin-walled adult type vessels is as yet unknown. But the analogy between those cases with anatomic obstruction between the pulmonary venous bed and the aortic valve—with consequent increase in the left atrial and pulmonary venous pressure—and the sequence of changes in mitral stenosis deserves emphasis. At least it

may be conjectured in these cases that the increased pulmonary arterial resistance of the fetus is sustained after birth because of the elevated pulmonary venous pressure. That medial thickening of the muscular pulmonary arteries is a relatively constant finding in congenital lesions of the left side of the heart, causing obstruction of pulmonary venous return, has been adequately demonstrated.[47]

By contrast, in preductal coarctation of the aorta, so long as the left ventricle remains competent, the left ventricular diastolic pressure and left atrial pressure may be expected to be normal. Thus a factor other than elevated pulmonary venous pressure must be looked for. The concept of the right ventricle as a common ejectile force for systemic (descending aortic) and pulmonary circulation is useful in this respect;[46] yet it sheds no light on why the pulmonary resistance remains elevated. That left ventricular failure is present at birth in some of these cases has been apparent from the clinical course; and in these cases at least, a mechanical stimulus to sustained elevation of pulmonary artery pressure may be delineated, and a parallel drawn to the development of pulmonary hypertension in adults in chronic left ventricular failure.

In isolated patent ductus arteriosus with reversed flow in infancy, the ductus apparently provides an avenue of escape for blood which could not successfully be expelled from the right ventricle through a narrowed pulmonary arterial bed without right heart failure; in coarctation, reverse ductal flow may protect the left ventricle from failure by diverting a large portion of the cardiac output to the lower portion of the body. Perhaps the only common design in the conditions in which right-to-left ductal flow persists is this: in no other way could blood leaving the right ventricle reach all or part of the systemic circulation without precipitating or increasing right or left heart failure.

That the ductus is not an effective method of sustaining life indefinitely in these circumstances is clear from the fact that the average duration of life of the 9 patients reviewed above was 13 months, and 3 died before the age of 1 month. But its usefulness as an "avenue of escape" may be discerned in older patients with patent ductus arteriosus and reversed flow: their clinical course may be relatively benign. By contrast, patients with primary pulmonary hypertension and pulmonary vascular resistance equivalent to that noted in patients with reversed ductal flow develop right heart failure rapidly and have a poor prognosis. This observation prompted an attempt to create a pulmonary artery-subclavian artery anastomosis in at least 1 patient with primary pulmonary hypertension, in an effort to provide a safety valve.[48]

2. *Persistence of the Veno-arterial Ductal Flow: Primary or Secondary?*

The concept outlined above of persistent fetal flow through the ductus in infancy as a *result* of distorted anatomy and physiology, rather than as a cause or a participating primary element in the malformation, deserves examination. It may be argued that, in coarctation of the aorta associated with the reversal of ductus flow, the failure of normal development of the left fourth branchial arch, which is relatively functionless in fetal life, and which gives rise to the isthmus of the aortic arch—the usual site of coarctation—is the *result* of persistent right-to-left flow through the ductus rather than the cause. Perhaps similarly the persistence of increased pulmonary resistance in isolated patent ductus arteriosus with reversal of flow is the *result* rather than the cause of the reversed shunt. This same approach cannot easily be held in the case of pulmonary venous or mitral and aortic valvular obstruction. In these cases, however, it can be said that the same disturbance in the development of the fetus that produced these anomalies causes the ductus to remain open.*

These points are not susceptible to ready answer. But it must be stressed that mos

*It is of interest in this regard that a background of maternal rubella is more common when patent ductus arteriosus co-exists with additional cardiac lesions than when patent ductus arteriosus is found as an isolated anomaly.[49]

ases in which the ductus remains patent in the absence of other anomalies are accompanied by left-to-right, rather than right-to-left shunts. In a minute fraction of cases, the right-to-left flow persists, and in virtually all of these, severe accompanying anomalies with a site of obstruction between the pulmonary origin of the ductus and the aortic insertion of the ductus are present. The inference seems proper that these additional anomalies influence the direction of flow.

In the fetal circulation, the ductus serves as a means of carrying pulmonary artery blood to the descending aorta, presumably because of the high resistance in the collapsed lungs. In most of the anomalies under discussion, a partial duplication of the fetal circulatory dynamics exists, in that resistance to the passage of blood through the pulmonary vessels and back to the left cardiac chambers is heightened. The ductus then would seem to be operating under the same general conditions that produce the fetal right-to-left shunt, and might be expected to sustain its fetal role.

A number of experimental avenues are open to investigation of the factors underlying persistence of the fetal ductus functions: (a) the artificial creation in the newborn animal of a zone of aortic stenosis proximal to the entrance of ductus arteriosus; (b) production of bilateral main pulmonary artery stenosis beyond the ductus: (c) production of pulmonary venous obstruction; (d) production of experimental mitral stenosis. The approach to all these procedures in the newborn dog suffers from the difficulty of sustaining life following this kind of surgery; in the attempt to create preductal coarctation, no dogs have yet survived. Efforts are underway, however, to explore this approach further. Another useful field of exploration involves the exposure of newborn dogs to chronic hypoxia in an effort to sustain fetal pulmonary hypertension and the right-to-left fetal ductus flow.

### *Increased Pulmonary Vascular Resistance*

Why does the pulmonary vascular resistance, high during fetal life, remain elevated after birth in this group of cases? The primary factor associated with most cases in which increased pulmonary resistance is found in man is probably a diminution in the cross-sectional area of the arterial bed (other factors such as increased length of arteries or increased viscosity of blood are certainly of less significance). Such a diminution may follow massive thrombosis or multiple emboli with a consequent decrease in the total number of functioning arteries, or it may be associated with decreased size of the vessels. Decreased vessel size may be related to vasoconstriction, or to organic alterations in the arterial wall. The latter include both medial muscular thickening—such as is found in the cases under discussion—and intimal thickening, usually found in the older age groups. That functional narrowing or vasoconstriction may play a role in pulmonary hypertension is now supported by a considerable body of evidence.[19, 22, 50–62]

An analysis of the general factors associated with increased pulmonary arterial resistance must include:

1. Obstruction to pulmonary venous outflow. The analogy to mitral stenosis and chronic left ventricular heart failure in adults with the associated development of pulmonary hypertension, has already been alluded to.

2. Elevated pulmonary blood flow. The association of increased resistance is inconstant in human subjects and need not depend on the size of the shunt.[65] Experimentally, it is possible to produce pulmonary hypertension and organic changes in the pulmonary arterial bed by creating large pulmonary artery aortic anastomoses in dogs and thus increasing pulmonary blood flow.[20] In the presence of persistent reversal of ductal flow in infancy, there is no good evidence that the pulmonary blood flow need be elevated.

3. Pulmonary parenchymal disease. This factor, operative in adults with severe chronic pulmonary disease,[21] might also apply to cases with congenital pulmonary disease and reversal of shunt.

4. Organic narrowing or occlusion of the pulmonary arteries, whether congenital[66] or due to thrombosis, multiple emboli, or atheromatous change.[67–69]

5. Hypoxia.[22, 50–55]

None of the foregoing factors is common to all conditions with reverse flow through the ductus in infancy. On the other hand, hypoxemia is present in all such anomalies. In two of these, isolated patent ductus arteriosus with reversal of flow and preductal coarctation with reversal of flow, the hypoxemia involves mainly the descending aorta and the lower portion of the body. Thus, both the thoracic sympathetic chain, which may be involved in nervous regulation of the pulmonary arteries,[58] and the bronchial arteries might be expected to be exposed to hypoxemia in virtually all of these lesions. Yet hypoxemia per se, as contrasted to alveolar hypoxia, clearly need not be associated with increased pulmonary resistance: in pulmonary arteriovenous fistulae, the tetralogy of Fallot and Ebstein's anomaly, the pulmonary artery pressure is usually normal.

Among those cases in which reversal of ductus flow persists in infancy, at least 1 type—congenital pulmonary disease associated with reversal of ductus flow—presents a possible cause of hypoxia. A striking aspect of cases with right-to-left ductal flow is that evidence of congestive heart failure appeared shortly after birth in most instances, as might be expected from the nature of the anomalies. Certainly in those cases with marked increase in pulmonary venous pressure, consequent engorgement of the lungs, and associated with a moderate degree of bronchospasm, a certain amount of hypoxia may be presupposed. If it is assumed that hypoxia may occur in these children at birth, associated with congestive heart failure, then perhaps this is a partial explanation of the stimulus for persistence of the high fetal pulmonary resistance. The suggestion has been made that an inborn difference in reactivity on the part of some individuals underlies their development of marked pulmonary hypertension as a response to stimuli that provoke no such profound change in others.[48]

4. *Therapeutic Implications*

Five cases of coarctation of the aorta c complete interruption of the isthmus with large distal ductus serving as the site of right-to-left shunt have been operated on at this institution, with 1 death. The other have either been significantly improved c cured. This is in marked contrast to the poo surgical experience in older patients wit reversal of flow through a ductus arteriosu in the absence of coarctation.

Case 9 is an example of this lesion, com plicated by a ventricular septal defect, i which surgical closure of the ductus and e cision of the coarcted segment were followe by improvement. The very high pulmonar artery pressure (113/35 mm. Hg) may wel have been related in large measure to the large ventricular septal defect. Since the patient has not yet been recatheterized, there is no way of knowing whether the pressure has remained at this level. In this case, it may be reasonably suggested that the ductus arteriosus, in spite of the right-to-left shunt, did not constitute a critical "avenue of escape." Closure at the time of coarctation repair failed to embarrass the right cardiac chambers, indicating that the resistance in the pulmonary vascular bed alone was not critical to continued functioning of the right ventricle. The additional possibility must be considered that left ventricular failure, elevated left ventricular diastolic pressure, and hence elevated left atrial and pulmonary venous pressure accompanied the coarctation, and contributed to the elevation of the pulmonary artery pressure as in chronic left ventricular failure in adults. Relief of the coarctation, then, diminished the burden on the left ventricle. This point of view is supported by the intractable heart failure prior to operation, and the relative clinical improvement since. Furthermore, the atresia of the isthmus may have acted to increase the left-to-right shunt through the ventricular septal defect. The major argument against this is the normal right ventricular diastolic pressure. In the presence of a large ventricular septal defect and left ventricular failure with elevated left ventricular diastolic pressure,

this should be reflected in an increased right ventricular diastolic pressure.

The experience with the cases of coarctation associated with reversed flow through the distal ductus suggests that the increased resistance in the pulmonary vascular bed is reversible in some of these cases. This may have significant implications for all lesions in which reversal of flow through the ductus is based on the primary increase in resistance beyond the pulmonary arteriolar bed. With the burgeoning of open heart surgery, complete correction for all these anatomic malformations may be feasible, and it seems reasonable to suppose that the closure of the ductus when normal anatomic channels elsewhere have been restored need not necessarily be a hazard in spite of the obvious increase in pulmonary resistance.


## Summary

In a number of different congenital cardiac anomalies, the ductus arteriosus serves as a site of continued fetal (veno-arterial) flow after birth. In all these conditions, the pulmonary arteriolar resistance must be significantly elevated to permit flow into the descending thoracic aorta. Beyond this, the common denominator of the malformations in which right-to-left flow persists is the presence of a site of obstruction to blood flow in the pulmonary vessels, left heart, or aorta at some point beyond the pulmonary origin of the ductus arteriosus but proximal to its aortic insertion. The ductus serves as an "avenue of escape" in most of these lesions: in no other way could blood leaving the right ventricle reach all or part of the systemic circulation without precipitating or increasing right or left heart failure. The anatomic basis of persistent fetal ductus function after birth, the factors involved in increased pulmonary arteriolar resistance in these anomalies, and the therapeutic implications of the surgical approach to a specific group of these cases are discussed.



## Acknowledgment

Many of the cases described in this paper were patients of Dr. Saul J. Robinson, who graciously permitted their inclusion. Cardiac catheterization studies were performed under the direction of Dr. Herbert Hultgren.



## Summario in Interlingua

In un numero de differente congenite anormalitates cardiac, le ducto arteriose servi como sito de un continuation postnatal del fetal fluxo veno-arterial. In omne iste conditiones le resistentia pulmono-arteriolar debe esser significativemente elevate pro permitter le fluxo a in le descendente aorta thoracic. In plus, un tracto commun del malformationes con persistentia del fluxo dextero-sinistre es le presentia de un sito de obstruction al fluxo sanguinee in le vasos pulmonar, le corde sinistre, o le aorta a un puncto trans le origine pulmonar del ducto arteriose sed cis su insertion aortic. In le majoritate de iste lesiones, le ducto servi como "via de escappamento," proque il existe nulle altere curso per que le sanguine veniente ab le ventriculo dextere pote attinger le complete circulation systemic o un parte de illo sin precipitar o augmentar disfallimento dextero-o sinistro-cardiac. Es discutite le base anatomic de persistentia del function del ducto fetal le nascentia, le factores que contribue al augmentate resistentia pulmono-arteriolar in iste anormalitates, e le valor therapeutic del tractamento chirurgic de un gruppo specific de casos.


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**Wyman, S. M.: Dissecting Aneurysm of the Thoracic Aorta: Its Roentgen Recognition.** Am. J. Roentgenol. **78**: 247 (Aug.), 1957.

This is a summary of 16 pathologically proved instances of aortic rupture with dissection where conventional roentgenograms of the chest were available for review. The most characteristic roentgenographic finding was a definite change in the diameter of the aorta occurring between 2 successive examinations. Increased prominence of either the ascending or descending portions of the aorta, particularly when associated with contour irregularities, also was highly suggestive of the diagnosis. Loss of clear contour formation was seen once; hemorrhage into the superior mediastinum, into the right middle lobe of the lung, and into the pericardium, once each. Plaques of calcium within the inner aspect of the aortic wall several millimeters from the outer margin provide reliable evidence of thickening of the aortic wall. The author indicates that conventional roentgenographic findings are often diagnostic. This does not imply that definite diagnosis cannot be established by other means (angiocardiography).

Schwedel

# Electrocardiographic Changes during Hemodialysis with the Artificial Kidney

*By* Albert L. Rubin, M.D., Glenn D. Lubash, M.D., Burton D. Cohen, M.D., David Brailovsky, M.D., Warren S. Braveman, M.D., and E. Hugh Luckey, M.D.

Rapid alteration of plasma electrolyte concentrations during dialysis with the artificial kidney may be associated with changes in the electrocardiogram and in cardiac function. In this study, the electrocardiographic changes encountered during 33 hemodialyses are described and correlated with abnormal electrolyte patterns and their correction.

EXTENSIVE studies provide the basis for correlating electrocardiograms with specific electrolyte abnormalities in clinical situations. The electrocardiogram has been of considerable value in the diagnosis and management of specific electrolyte imbalance. Hemodialysis with the artificial kidney permits the study of the electrocardiogram during changing electrolyte patterns in the patient with renal disease and the uremic syndrome. The marked alterations in electrolyte concentrations occasionally occurring during dialysis may induce changes in the electrocardiogram and cardiac function which constitute a hazard to the patient.[1, 2] At frequent intervals during the course of 33 dialyses in 28 patients, we have had the opportunity to correlate the electrocardiographic changes with the plasma electrolyte concentrations. This report summarizes our experience.

## Materials and Methods

The dialyses were performed on 12 female and 16 male patients at Bellevue Hospital, The New York Hospital, and the Veterans Administration Hospital, New York City. The patients ranged in age from 10 to 74, with an average of 41 years. The indication for dialysis was acute renal failure in 10 patients and severe symptomatic chronic uremia in 16 patients. One patient with multiple myeloma was treated by dialysis in an attempt to correct hypercalcemia and 1 patient was treated because of symptomatic biliary cirrhosis. Digitalis had been administered to 4 of the patients with acute renal failure, to 7 of the patients with chronic uremia, and to 1 of the other 2 patients.

Hemodialysis was performed with a disposable twin-coil artificial kidney.[3, 4] In most instances the procedure lasted 6 hours, in several 8 or 10 hours, and in 1 patient 12 hours.

Simultaneous blood specimens were collected from the patient and from the tubing returning blood to the patient from the dialysis unit. Specimens were drawn at 2-hourly intervals or more frequently when indicated by electrocardiographic changes. Plasma was separated at once and frozen for later analysis. The concentrations of sodium, chloride, potassium, carbon dioxide combining power, and osmolality were determined. Blood urea nitrogen values and weights were recorded before and after dialysis in most patients. Calcium and phosphorus determinations were done in selected patients.

Electrocardiograms were recorded by a direct writing portable machine every 2 hours and more frequently when irregularities in rhythm were noted on clinical examination. Laboratory methods for determination of plasma sodium, chloride, potassium, and carbon dioxide combining power have been described previously.[5] Osmolality was determined by a Fiske Osmometer.

## Results

The values for plasma electrolytes, blood urea nitrogen, serum calcium and phosphorus, and body weights are presented in table 1. In 14 of the 33 studies the plasma potassium concentration was elevated above 5.5 mEq. per L. prior to dialysis. In most patients acidosis, hyponatremia, hypochloremia, and

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TABLE 1.—*Values of Plasma Electrolyte, Blood Urea Nitrogen, Serum Calcium and Phosphorus, and Body Weights at the Start and End of Dialysis*

| Patient | START OF DIALYSIS | | | | | | | | | END OF DIALYSIS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | mEq/L | | | mM/L | | | mgm% | | Wt | mEq/L | | | mM/L | | | mgm% | | Wt |
| | K | NA | CL | $CO_2$ | Osmolality | BUN | CA | P | Kgm | K | NA | CL | $CO_2$ | Osmolality | BUN | CA | P | Kgm |
| 1 | 6.5 | 138 | 103 | 8.5 | 368 | 134 | | | | 5.0 | 143 | 92 | 11.7 | 301 | 118 | | | |
| 2 | 5.3 | 140 | 93 | 12.6 | 298 | 78 | 5.5 | 4.5 | 73.6 | 5.9 | 144 | 113 | 25.1 | 295 | 30 | 10.6 | 4.6 | 70.9 |
| 3 | 4.4 | 132 | 83 | 31.3 | 332 | 150 | | | 53.0 | 4.5 | 147 | 112 | 23.8 | 307 | 92 | | | |
| 4 | 3.3 | 134 | 93 | 4.9 | 345 | 156 | 9.7 | 10.4 | 70.0 | 3.3 | 146 | 107 | 18.1 | 345 | 72 | 9.0 | 5.4 | |
| 5 | 7.4 | 138 | 100 | 10.8 | 369 | 247 | 8.4 | 5.8 | 59.5 | 4.9 | 144 | 106 | 22.3 | 315 | 60 | | | 54.6 |
| 6 | 5.5 | 120 | 81 | 15.8 | 291 | 104 | | | 58.2 | 3.7 | 138 | 103 | 18.6 | 293 | 25 | | | 56.4 |
| 7 | 5.9 | 133 | 95 | 15.3 | 306 | 80 | | | 57.3 | 3.8 | 143 | 105 | 23.0 | 300 | 23 | | | 55.4 |
| 8 | 7.2 | 126 | 93 | 9.4 | 342 | | | | 64.1 | 4.4 | 134 | 103 | 17.6 | 311 | | | | 63.2 |
| 9 | 4.2 | 139 | 98 | 15.4 | 344 | 150 | | | 54.1 | 4.3 | 144 | 108 | 25.6 | 313 | | | | 52.3 |
| 10 | 4.6 | 140 | 108 | 24.7 | 287 | 15 | | | 51.0 | 4.4 | 143 | 110 | 25.5 | 288 | | | | 51.4 |
| 11 | 7.1 | 130 | 100 | 17.5 | 299 | 18 | 15.1 | 5.5 | 85.0 | 5.7 | 133 | 99 | 23.7 | 299 | | 12.0 | | |
| 12 | 7.5 | 109 | 82 | 7.4 | 275 | 95 | | | 62.5 | 4.3 | 127 | 98 | 19.0 | 280 | 54 | | | 60.5 |
| 13 | 4.7 | 128 | 92 | 13.6 | 292 | 101 | | | 67.9 | 3.9 | 134 | 103 | 18.9 | 285 | 56 | | | |
| 14 | 4.0 | 142 | 108 | 9.5 | 341 | 138 | | | 65.9 | 3.5 | 140 | 108 | 21.2 | 305 | 95 | | | 62.3 |
| 15 | 5.5 | 136 | 80 | 11.8 | 370 | 234 | | | 65.0 | 3.9 | 138 | 105 | 22.5 | 313 | 75 | | | 62.7 |
| 16 | 5.7 | 138 | 86 | 9.4 | 418 | 200 | 7.4 | | 68.2 | 3.4 | 140 | 107 | 19.9 | 316 | | | | 67.7 |
| 17 | 5.7 | 129 | | 24.0 | | 50 | 5.6 | | | | | | | | | | | |
| 18 | 4.5 | 130 | 108 | 13.2 | 322 | 125 | 6.8 | 9.3 | 45.9 | 4.1 | 137 | 106 | 23.1 | 292 | 46 | | | 47.7 |
| 19 | 6.4 | 146 | 108 | 9.0 | 390 | 188 | 7.4 | 15.9 | 50.0 | 3.4 | 142 | 110 | | 350 | 80 | | | |
| 20 | 6.1 | 133 | 107 | 3.2 | 343 | 174 | | | 60.7 | 4.3 | 137 | 107 | 8.8 | 303 | 138 | | | 58.0 |
| 21 | 4.6 | 141 | 82 | 13.4 | 408 | 234 | | | 52.0 | 3.7 | 139 | 99 | 15.5 | 344 | | | | 51.5 |
| 22 | 5.1 | 147 | 100 | 14.3 | 391 | 228 | | | 50.0 | 4.4 | 144 | 106 | 21.3 | 325 | | | | |
| 23 | 4.3 | 134 | 98 | 11.8 | 342 | 150 | 8.9 | 9.5 | 71.8 | 4.5 | 142 | 106 | 18.5 | 321 | 69 | 11.8 | 6.9 | 71.1 |
| 24 | 3.2 | 129 | 80 | 19.8 | 331 | 180 | 7.8 | 16.0 | 58.7 | 4.7 | 144 | 106 | 18.5 | 308 | 28 | 12.5 | 9.5 | 51.7 |
| 25 | 7.7 | 123 | 78 | 7.6 | 338 | 159 | 9.0 | | 77.7 | 4.7 | 135 | 98 | 18.4 | 320 | 100 | 9.1 | 13.5 | 72.0 |
| 26 | 7.4 | 129 | 104 | 8.4 | 332 | 127 | | | 35.9 | 3.0 | 138 | 108 | 20.3 | 300 | 57 | | | 35.0 |
| 27 | 7.4 | 134 | 108 | 11.7 | 308 | 88 | | | | 4.1 | 138 | 108 | 21.8 | 300 | 31 | | | 35.0 |
| 28 | 6.1 | 128 | 95 | 15.4 | 310 | 109 | 8.4 | 4.4 | 35.9 | 4.1 | 142 | 110 | 23.4 | 303 | 47 | 8.8 | 4.4 | 33.6 |
| 29 | 4.7 | 131 | 94 | 11.7 | 335 | 260 | 9.7 | 6.8 | 59.3 | 3.7 | 141 | 108 | 18.5 | 297 | 36 | 9.6 | 3.7 | 58.5 |
| 30 | 4.0 | 134 | 87 | 14.6 | 349 | 345 | 7.4 | 13.5 | 93.6 | 3.8 | 137 | 101 | 18.8 | 321 | 108 | 9.5 | 9.7 | 93.2 |
| 31 | 6.3 | 150 | 109 | 18.7 | 385 | 105 | | | 65.7 | 3.7 | 148 | 109 | 22.2 | 334 | 63 | | | 63.9 |
| 32 | 6.5 | 105 | 80 | 4.0 | 405 | 210 | 5.4 | 19.8 | 65.3 | 2.3 | 128 | 92 | 9.0 | 329 | 112 | | | 66.5 |
| 33 | 4.7 | 125 | 93 | 17.8 | 326 | 122 | 8.1 | 10:5 | 75.2 | 4.5 | 136 | 104 | 22.1 | 320 | 70 | 9.8 | 7.7 | 74.4 |

TABLE 2.—*Classification of Diagnosis, Digitalis Administration, and Electrocardiographic Changes Associated with Dialysis*

| | Patient | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1* | 2* | 3 | 4 | 5 | 6* | 7* | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | Total |
| Diagnosis | C | C | C | C | C | C | C | C | C | O | O | A | C | C | A | A | A | C | C | A | A | A | C | C | C | A | A | A | C | A | A | A | C | |
| Digitalis | + | | + | | + | | | | | | + | | | + | | | | + | | + | | | + | + | + | + | + | + | | + | + | | | 15 |
| **EKG at Start of Dialysis** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Normal | | | | + | | | | | | + | | | + | | | | | | | | | | | + | | | | | | | | + | 5 |
| Suggests Hyperpotassemia | | | | | | | | + | | | | + | | | + | + | | | | | + | | | | | | | | | | + | | | 6 |
| T Wave Abnormalities | | | | | + | | | | | | | | | | | | | | | | | | | | | | | + | | | | | | 2 |
| ST-T Wave Abnormalities | | | | | | | | | + | | + | | | | | | | + | + | | + | | + | + | | | + | + | + | | | + | | | 11 |
| LVH | +** | | + | | | | | | | | | | | + | | | | | | + | | | | | + | | | | | + | | | | 6 |
| **EKG Change During Dialysis** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| No Change | | | | + | | +* | +* | | + | + | + | | + | | | | + | | | | | | + | | | | | | | | | | + | 10 |
| Regression of Hyperpotassemia | | | | | | | | + | | | | + | | | + | + | | | | | + | | | | | | | | | | + | | | 6 |
| ST-T Wave Alterations | | | + | | + | | | | | | | | | + | | | | | + | + | + | | + | | + | + | + | + | + | + | + | | | 15 |
| Arrhythmia | + | + | + | | + | | | | | | | | + | | | | | | | + | | | | | | + | + | | + | + | + | | | 11 |

Diagnosis: A= Acute Uremia, C= Chronic Uremia, O= Other

* Complete EKGs not taken during dialysis. ** EKG prior to dialysis

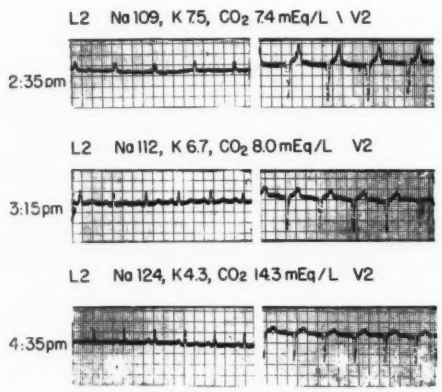



FIG. 1. Note change in peaked T waves, widened QRS complex, and atrial arrest during dialysis with correction of hyperpotassemia, hyponatremia, and acidosis.

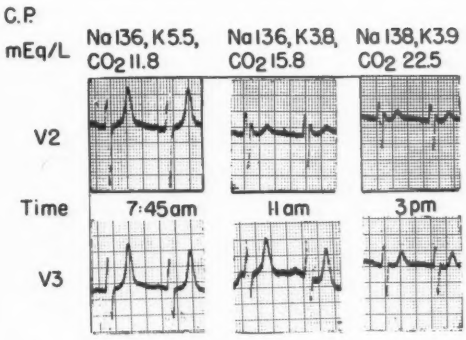



FIG. 2 *Top.* Note change in peaked T waves with correction of acidosis and slight hyperpotassemia during dialysis.

FIG. 3 *Bottom.* Note appearance of ST-wave depression as hypocalcemia was corrected during dialysis. The patient had received digitalis. The increase in ventricular rate does not account for the degree of change.

hypocalcemia were also present at the start of dialysis.

The electrocardiogram showed normal sinus rhythm in 31 of 33 instances at the start of dialysis. The 2 exceptions were 1 patient with atrial tachycardia and another with atrial arrest with a nodal pacemaker. Table 2 presents data to correlate the diagnosis, digitalis administration, initial electrocardiographic form, and changes during dialysis. The electrocardiographic patterns may be divided into 4 groups.

Group 1. Dialysis was associated with no changes in the form of the electrocardiogram. This occurred in 8 dialyses. Digitalis had been administered to only 2 of these patients. Plasma potassium concentration was elevated in only 2 patients in this group.

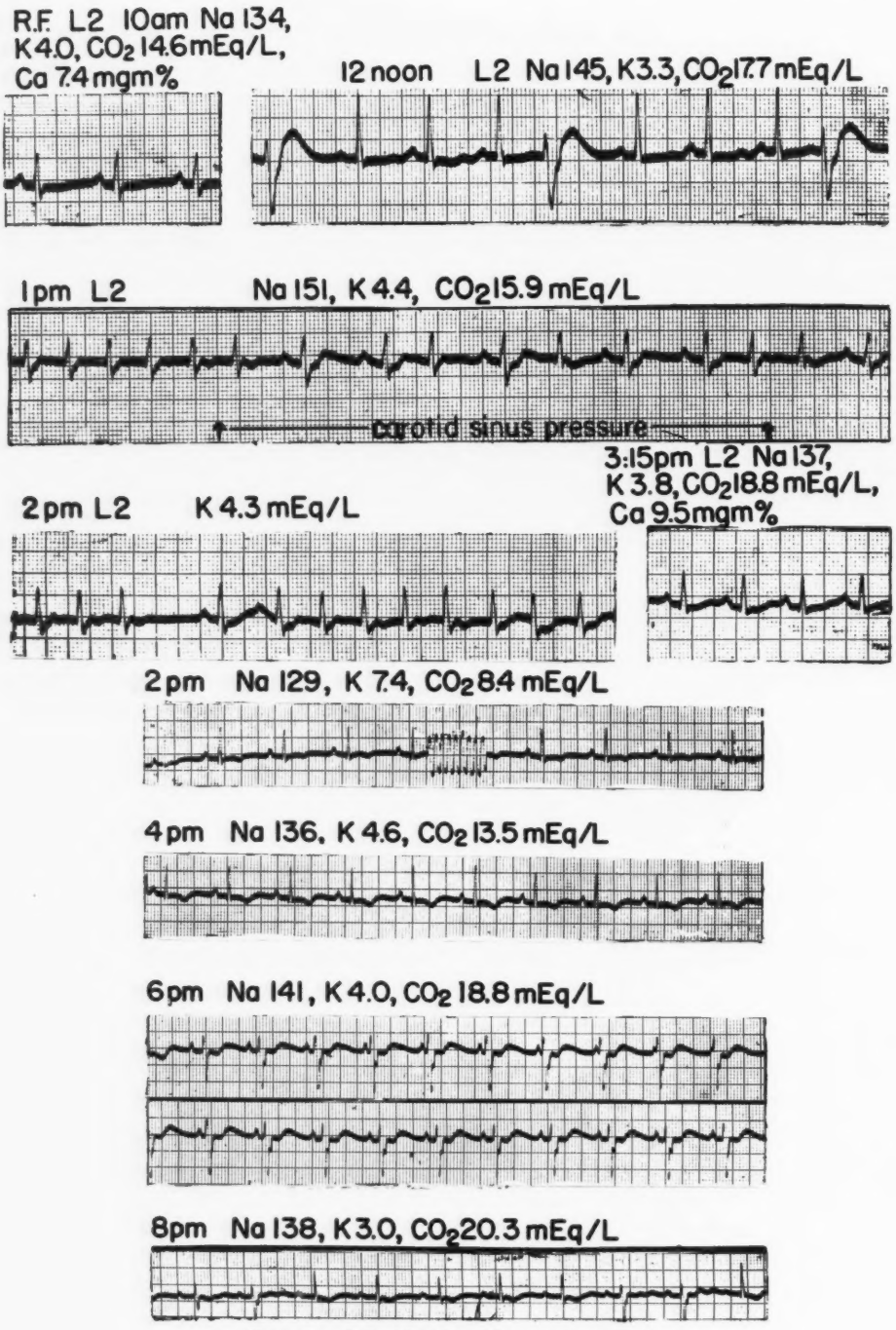
Group 2. Dialysis was associated with T-T wave alterations consistent with regression of hyperpotassemia. This change was noted during the course of 6 dialyses. In 1 patient, J.H. (case 12, fig. 1), the electrocardiogram showed atrial arrest, slight widening of the QRS complex, and peaked T waves. These changes disappeared during dialysis. No patient in this group had received digitalis. In 10 other instances, hyperpotassemia was present without suggestive electrocardiographic changes. The absence of typical changes of hyperpotassemia may have been due to a basic abnormality in the electrocardiogram, since digitalis had been administered to 8 of these patients. One patient not receiving digitalis had electrocardiographic changes compatible with left ventricular hypertrophy. The remaining patient (case 17) had electrocardiographic changes consistent with hypotension, which persisted throughout the procedure.

Typical changes during regression of hyperpotassemia were seen in case 15.

*Case 15.* C. P. a 42-year-old white man with carbon tetrachloride intoxication and acute renal failure was subjected to dialysis because of electrocardiographic changes consistent with hyperpotassemia. These regressed during dialysis (fig. 2). It is noteworthy that the initial potassium elevation was slight. The electrocardiographic pattern probably reflected the contribution of other electrolyte abnormalities.

Group 3. Dialysis was associated with ST-T wave alterations suggestive of digitalis effect. ST wave depression occurred in 15 instances. In 13 of these, digitalis had been administered prior to dialysis.

*Case 24.* P. D. a 42-year-old white man with chronic uremia due to polycystic kidney disease had received digitalis prior to dialysis. During


R.F. L2 10am Na 134, K 4.0, $CO_2$ 14.6 mEq/L, Ca 7.4 mgm%
12 noon L2 Na 145, K 3.3, $CO_2$ 17.7 mEq/L
1pm L2 Na 151, K 4.4, $CO_2$ 15.9 mEq/L
carotid sinus pressure
3:15pm L2 Na 137, K 3.8, $CO_2$ 18.8 mEq/L, Ca 9.5 mgm%
2pm L2 K 4.3 mEq/L
2pm Na 129, K 7.4, $CO_2$ 8.4 mEq/L
4pm Na 136, K 4.6, $CO_2$ 13.5 mEq/L
6pm Na 141, K 4.0, $CO_2$ 18.8 mEq/L
8pm Na 138, K 3.0, $CO_2$ 20.3 mEq/L

FIGS. 4 and 5. (*See legend opposite page.*)

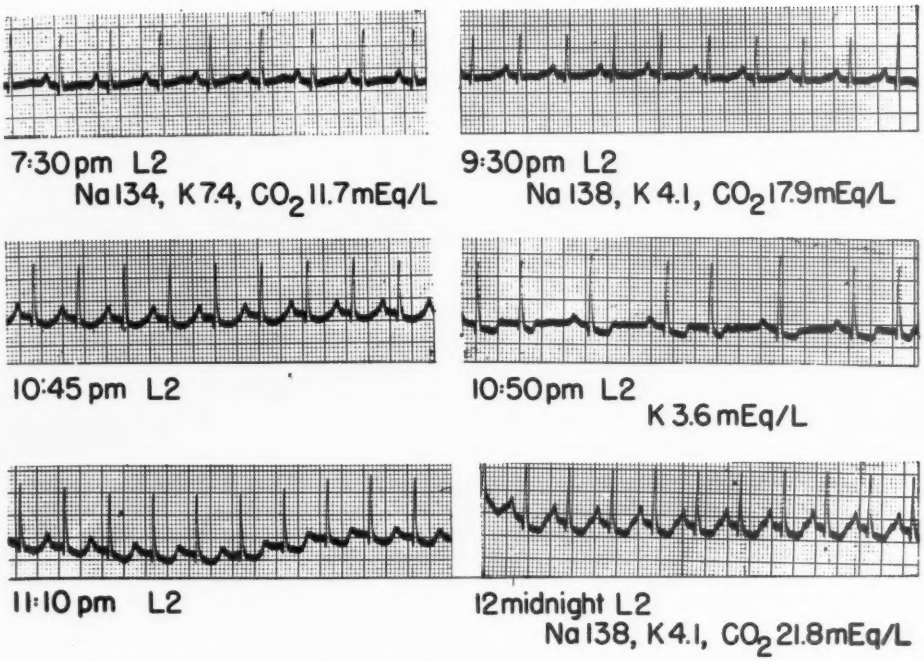



FIG. 6. Note appearance of paroxysmal atrial tachycardia with block (10:50 p.m.) in a digitalized patient with correction of hyperpotassemia and acidosis during dialysis. Thirty grams of potassium chloride were added to the bath immediately and at 11:10 p.m. the rhythm was sinus tachycardia, which gradually slowed.

dialysis, ST-T changes appeared as hyponatremia and hypocalcemia were corrected (fig. 3).

One patient who had not received digitalis was hypotensive throughout the procedure, an adequate explanation for the S-T depression. This patient died shortly after dialysis. In 1 patient no explanation for the ST-T wave changes is available.

Group 4. Dialysis was associated with an arrhythmia (table 3). Ventricular premature contractions during dialysis occurred in 4 patients. In 3 of these, the arrhythmia could not be related to electrolyte changes or to digitalis toxicity. In the fourth patient, ventricular premature contractions in a quadrigeminy pattern preceded paroxysmal atrial tachycardia with block and was considered to be due to digitalis toxicity.

*Case 30.* R. F. a 42-year-old white man had severe uremic symptoms secondary to subacute glomerulonephritis. Digitalis had been administered prior to dialysis and the electrocardiogram was consistent with left ventricular hypertrophy. The significant electrolyte alteration during dialysis was a rise in calcium. Ventricular premature

FIG. 4 *Top.* Note appearance of ventricular premature contractions (12 noon) in a digitalized patient in association with correction of acidosis and lowering of plasma potassium during dialysis. This was followed by the appearance of paroxysmal atrial tachycardia with block (1:00 p.m.), which disappeared (3:15 p.m.) without addition of potassium to the dialyzing bath. Note the rise in serum calcium during the procedure.

FIG. 5 *Bottom.* Representative leads II during dialysis in which hyperpotassemia and acidosis were corrected. The patient had received digitalis. At 6:00 p.m. wandering of the pacemaker into the A-V node or A-V dissociation appeared. Twenty grams of potassium chloride were added to the bath at 6:45 p.m. and at 8:00 p.m. the electrocardiogram showed normal sinus rhythm.

TABLE 3.—*Summary of Arrhythmias That Appeared During Dialysis. Digitalis Administration is Noted*

| Arrhythmias | Patient | | | | | | | | | | | Tota |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 5 | 13 | 19 | 26 | 27 | 29 | 30 | 31 | |
| Digitalis | + | | + | + | | | + | + | | + | + | 7 |
| Ventricular premature contractions | | | + | | + | | | | + | + | | 4 |
| Atrial premature contractions | | | + | + | | | | | | | | 2 |
| Atrial fibrillation | | | | | | + | | | | | | 1 |
| Nodal rhythm | + | + | | + | | | + | | | | + | 5 |
| Paroxysmal atrial tachycardia | | | | | | | | + | | + | | 2 |

contractions were noted followed by paroxysmal atrial tachycardia with atrioventricular (A-V) block (fig. 4). This change may have resulted from the acute correction of hypocalcemia. Potassium was not added to the dialysis bath and the changes disappeared.

Nodal rhythm occurred in 5 patients, 4 of whom had received digitalis. In these 4 the rhythm was thought to be secondary to effects of digitalis revealed by correction of electrolyte changes (lowering of potassium and correction of acidosis). Addition of potassium to the dialysis bath effectively restored normal sinus rhythm. In the fifth patient (case 2) nodal rhythm was transient. The rhythm was atrial tachycardia at the start of dialysis and was atrial fibrillation at the end.

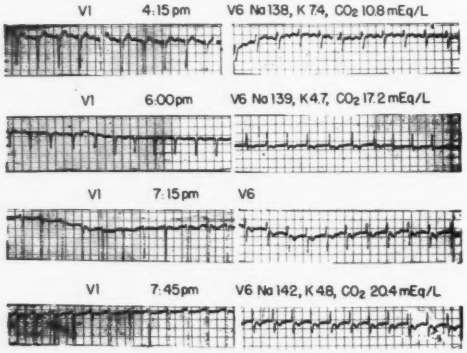



FIG. 7. Note appearance of nodal tachycardia (6:00 p.m.) during dialysis in association with correction of hyperpotassemia and acidosis. The patient had received digitalis. At 6:15 p.m. 30 Gm. of potassium chloride were added to the bath and at 7:15 p.m. the rhythm was normal sinus, initially with first-degree heart block. Note that the plasma potassium at 7:45 p.m. was unchanged from that at 6:00 p.m.

C. O., a 10-year-old white girl was treated by dialysis on 3 occasions because of hyperpotassemia and severe uremia due to acute nephritis. Digitalis had been administered. During the first dialysis (case 26), there was wandering of the pacemaker from the sinus node to the AV node and within the AV node or AV dissociation (fig. 5). During the second dialysis (case 27), the patient developed paroxysmal atrial tachycardia with block (fig. 6). Addition of potassium to the bath reversed the changes on each occasion.

*Case 5.* E. K. a 16-year-old white woman with chronic pyelonephritis was subjected to dialysis because of severe uremic symptoms. She had received digitalis and the initial electrocardiogram revealed T-wave abnormalities. During dialysis nodal rhythm developed. After addition of potassium to the bath normal sinus rhythm returned, initially with first degree heart block (fig. 7).

## DISCUSSION

Hyperpotassemia classically produces elevation and peaking of the T waves followed by prolongation of the QRS complex and disappearance of the P waves.[6-8] Such electrocardiographic changes have been shown to correlate only roughly with measured concentrations of plasma potassium, and even this correlation is possible only at extreme concentrations.[9, 10]

The electrocardiogram in hypocalcemia may show QT-interval prolongation due mainly to alterations in the S-T segment,[7, 11, 12] and the reverse may be true in hypercalcemia.[13]

Rarely do these abnormalities occur singly. More often complex acid-base and electrolyte abnormalities accompany them and modify or exaggerate the electrocardiographic effects of a specific level of potassium[14, 15] or calcium.

The complex relationships of the electrocardiogram to the measured concentrations of potassium, sodium, calcium, and carbon dioxide combining power (reflecting acidosis) are evident from the data presented. In addition, the effect of potassium appears to be modified if the electrocardiogram is basically abnormal.[6-8, 16, 17] Moreover, hemodialysis tends to correct many existing electrolyte abnormalities. Equilibrium across the membrane is probably achieved at varying rates, dependent on variations in exchange gradients and available ion stores. Anticipated electrocardiographic patterns are thus often lacking before and during dialysis. Figures 1 to 7 have been chosen to illustrate the complexity of these relationships.

Plasma electrolyte concentration poorly reflects intracellular ion concentration; nor have attempts to correlate the intracellular electrolyte concentration with the electrocardiogram proved more reliable.[7] During dialysis, ion exchange across the cellular membrane can be postulated. In several instances electrocardiographic changes appeared and were reversed by adding potassium to the dialyzing bath without significant change in plasma values. The speed of exchange at the cellular membrane is probably also important. In case 26 (fig. 5) signs of digitalis toxicity appeared when the plasma potassium concentration was 4.0 mEq. per L. and disappeared with the addition of 20.0 Gm. of potassium chloride to the bath. However, at the end of dialysis the plasma potassium concentration was even lower, 3.0 mEq. per L., than that at which digitalis toxicity had been manifest. Addition of potassium to the bath may have slowed or even reversed exchange across the cellular membrane.

The interaction of digitalis and potassium acting on the AV node is demonstrated in figures 6 and 7. In each instance, the addition of potassium to the dialyzing bath reversed signs of digitalis toxicity.

In the patient with heart disease who receives digitalis, electrolyte changes assume particular significance during hemodialysis. The appearance of enhanced digitalis effects and toxicity under these circumstances has been described by several observers.[1,2] This may result from lowered plasma potassium, correction of acidosis, and elevated calcium level, or all 3. It is not known whether dialysis will decrease total body stores of digitalis.

Because of the occurrence of adverse cardiac effects, particularly in the patient with heart disease, frequent electrocardiographic observations are warranted during the course of hemodialysis.


## Summary

Extracorporeal hemodialysis employing the disposable coil artificial kidney affords an excellent opportunity for electrocardiographic study during changing electrolyte patterns. Electrolyte data are presented in 28 patients during the course of 33 dialyses and alterations are correlated with the electrocardiogram. The data reemphasize that in most clinical situations electrocardiographic changes are rarely associated with specific electrolyte concentrations and abnormalities.

In the patient who has received digitalis prior to dialysis, frequent electrocardiographic observations during dialysis are necessary to detect and prevent serious digitalis intoxication.

## Summario in Interlingua

Le hemodialyse extracorporee per medio del ren artificial (typo a serpentino non reusabile) offere un excellente opportunitate pro studios electrocardiographic durante cambiante configurationes electrolytic. Es presentate datos relative al electrolytos observate in le curso de 33 dialyses in 28 patientes, e le alterationes es correlationate con le electrocardiogramma. Le resultatos signala de novo que in le majoritate del situationes clinic, alterationes electrocardiographic es rarmente associate con specific concentrationes del electrolytos o con specific anormalitates in illos.

In patientes qui ha recipite digitalis ante le tempore del dialyse, frequente observationes electrocardiographic es necessari durante le curso del dialyse a fin de deteger e prevenir serie intoxication per digitalis.

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# Effects of Racemic Epinephrine Inhalation on Cardiopulmonary Function in Normal Man and in Patients with Chronic Pulmonary Emphysema

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Epinephrine inhalation is now widely used to provide bronchodilator therapy for patients with chronic obstructive pulmonary emphysema. In this study a variety of cardiorespiratory effects following epinephrine inhalation have been examined to compare responses in normal and emphysematous subjects, and to evaluate possible differences between inhalational and parenteral usage of the drug. Since previous studies on the effects of epinephrine in emphysematous patients have been largely concerned with the respiratory apparatus, particular attention here has been directed toward the pulmonary circulation.

CLINICAL management of patients with chronic obstructive pulmonary emphysema at present frequently involves use of an effective bronchodilator agent delivered via an effective route. Epinephrine, administered by the inhalation of a nebulized solution, continues to be one of the most widely used agents. It therefore seemed desirable to compare the effects of epinephrine inhalation with those known to occur following parenteral administration in man, and to compare the drug responses in normal and emphysematous subjects. Observations on a variety of cardiorespiratory effects following epinephrine inhalation, with particular attention to the pulmonary circulation, constitute the basis of this report.

The data presented are from studies carried out in 5 healthy normal subjects, and in 11 patients with chronic pulmonary emphysema of varying severity. In each instance in the latter group the diagnosis of pulmonary emphysema was made on the basis of characteristic clinical findings, roentgenograms of the chest, and standard pulmonary function tests. In order to define the degree of severity of the disease process from a functional viewpoint, the emphysematous patients were grouped into 4 categories according to the criteria of Baldwin, Cournand, and Richards.[1] In table 1 is a list of the symbols and abbreviations used in presenting the physiologic data in subsequent tables. In table 2 are shown the physiologic groups into which the emphysematous patients fell, together with data on pulmonary function relative to lung volumes and intrapulmonary gas mixing. Of the emphysematous subjects, 2 fell into group 1, 2 into group 2, and the remaining 7 into group 3. In all cases except 1 (V.G.), the index of intrapulmonary gas mixing was elevated above the upper limit of normal (2.5 per cent). In all cases but 1 (R.G.), the ratio of the residual volume to total capacity of the lung was elevated well above the predicted normal value. In this patient, however, there was present in addition to the emphysematous process moderately advanced pulmonary fibrosis and chronic bronchiectasis as shown by histologic examination of a resected lobe of the lung following this study.

## METHODS

The pharmacologic agent used in this study was a 2.25 per cent solution of racemic epinephrine,* administered by oral inhalation of the nebulized solution. This was carried out by manual operation of a rubber bulb hand-pump nebulizer held about 1 inch from the open mouth of the subject.

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*Kindly supplied as Vaponefrin by the Vaponefrin Company, Upper Darby, Pa.

TABLE 1.—*Symbols*

| | |
|---|---|
| B.S.A. | Body surface area, square meters. |
| $V_E/M^2$ | Ventilation, liters per minute BTPS, per square meter of body surface area. |
| $V_{O_2}/M^2$ | Oxygen uptake, milliliters per minute STPD, per square meter body surface area. |
| $_pH_s$ | Arterial blood pH (serum). |
| $S_{aO_2}$ | Oxygen saturation, arterial blood, per cent. |
| $P_{aCO_2}$ | Carbon dioxide tension, arterial blood, millimeters of mercury. |
| HPM | Index of intrapulmonary gas mixing (alveolar nitrogen concentration after 7 minutes of pure oxygen breathing). |
| $\frac{RV}{TC}$ | Residual volume to total capacity ratio. |
| f | Respiratory frequency as breaths per minute. |
| $V_T$ | Tidal volume, milliliters BTPS. |
| $R_E$ | Respiratory exchange ratio (RQ), expired air. |
| $V_{DCO_2}$ | Physiological (Bohr) dead space to carbon dioxide, milliliters BTPS, personal. |
| VC | Vital capacity, milliliters BTPS. |
| MBC | Maximum breathing capacity, liters per minute BTPS. |
| HR | Heart rate, beats per minute. |
| CI | Cardiac index (cardiac output, liters per minute, per square meter body surface area). |
| SV | Stroke volume. |
| $C_{aO_2}-C_{vO_2}$ | Arteriovenous difference in oxygen content. |
| S | Systolic. |
| PP | Pulse pressure. |
| D | Diastolic. |
| M | Mean. |
| WP | Wedge pressure. |
| SVRI | Systemic vascular resistance index (systemic vascular resistance in dyne-second-cm. $-^5$ per square meter body surface area). |
| PVRI | Pulmonary vascular resistance index (pulmonary vascular resistance in dyne-second-cm. $-^5$ per square meter body surface area). |
| $P_{IE}$ | Intra-esophageal pressure. |

Right heart catheterization was carried out in all subjects in the postabsorptive state. Control observations were carried out over a period of approximately 1 hour. These included multiple records of vascular pressures at rest with the patient breathing room air, and 2 separate determinations of the cardiac output by the method based upon the Fick principle. Cardiac output determinations were made over a 3-minute period

TABLE 2.—*Physiologic Classification of Emphysematous Subjects, with Data Relative to Lung Volumes, and the Effect of Racemic Epinephrine Inhalation upon Vital and Maximum Breathing Capacities**

| Subject | Age | B.S.A. | HPM | RV/TC | Status | Vital Capacity | Maximum breathing capacity |
|---|---|---|---|---|---|---|---|
| Group 1 | | | | | | | |
| E.S. | 78 | 1.60 | ..... | .. | Rest | ..... | .. |
| | | | | | p epinephrine | ..... | .. |
| J.K. | 37 | 1.70 | 4.76 | 46 | Rest | 3,620 | .0 |
| | | | | | p epinephrine | ..... | .. |
| Group 2 | | | | | | | |
| V.G.† | 29 | 1.68 | 2.15 | 49 | Rest | 1,857 | .6 |
| | | | | | p epinephrine | 2,037 | 39 |
| R.G. | 15 | 1.40 | 4.09 | 21 | Rest | 2,800 | .6 |
| | | | | | p epinephrine | 3,418 | 96 |
| Group 3 | | | | | | | |
| P.M. | 68 | 1.61 | 8.75 | 69 | Rest | 1,304 | 23 |
| | | | | | p epinephrine | 1,350 | 23 |
| C.D. | 51 | 1.73 | 4.52 | 62 | Rest | 2,079 | 19 |
| | | | | | p epinephrine | 2,900 | 22 |
| G.A. | 65 | 1.75 | 9.98 | 62 | Rest | 2,360 | 22 |
| | | | | | p epinephrine | 2,816 | 28 |
| C.T. | 60 | 1.68 | 5.22 | 60 | Rest | 1,800 | 36 |
| | | | | | p epinephrine | 2,960 | 33 |
| J.B. | 49 | 1.58 | 5.48 | 54 | Rest | 1,010 | 44 |
| | | | | | p epinephrine | 1,184 | 36 |
| W.R. | 66 | 1.82 | 15.76 | 64 | Rest | 2,50- | 30 |
| | | | | | p epinephrine | 3,400 | 38 |
| E.L. | 53 | 1.81 | 9.8 | 68 | Rest | 1,216 | 10 |
| | | | | | p epinephrine | 1,592 | 24 |

* Lung volumes are reported in ml., BTPS.
† Female, all others male.

in each instance, ventilation and oxygen uptake being measured for this whole interval, and samples of arterial and mixed venous blood being collected from the pulmonary artery simultaneously during the middle minute. Following this, the patient inhaled the nebulized racemic epinephrine solution for several breaths at a time alternating with brief rest periods for a total of 10 to 15 minutes, during which period further observations on vascular pressures were made. In each study about 1 ml. of the racemic epinephrine solution was nebulized and inhaled. This is at least 2 or 3 times the usual dosage that might be administered therapeutically at a given time to an emphysematous patient. It is not known exactly how much of this aerosol may have reached the alveoli, or how much may have been absorbed through the pulmonary epithelium or through the epithelium of the upper respiratory tract. Cardiac output determinations were made in most instances within 15 to 25 minutes after administration of racemic epinephrine was started, and within 10 minutes after inhalation of the agent was completed.

Ventilation was measured by means of a Tissot Gasometer of 120-liter capacity with kymographic drum to record respiratory frequency. Gas samples were collected over mercury for analysis of carbon dioxide and oxygen content in the Scholander gas analyzer.

Arterial blood pH was determined at 37 C. in a glass electrode pH meter within 10 minutes after the drawing of the blood sample. Arterial blood carbon dioxide content, oxygen content, and oxygen capacity were determined with the Van Slyke manometric apparatus. Arterial serum carbon dioxide content and carbon dioxide tension were calculated from the Henderson Hasselbalch nomograms, from whole blood carbon dioxide content, oxygen saturation and capacity, and serum pH. Physiologic dead space to carbon dioxide was calculated from the Bohr formula,[2] with the assumption of carbon dioxide tension as equivalent to mean alveolar carbon dioxide tension, and with 60 ml. subtracted for instrumental dead space to give a value for personal dead space.

Records of air flow velocity at the mouth were obtained by means of a Silverman-type pneumotachometer with strain-gage pressure transducer, amplifier, and electronic recorder. To measure intraesophageal pressure, a thin-walled rubber balloon on the end of a narrow plastic tube was introduced through the nose into the esophagus, so that the tip of the balloon rested in the lower third of the esophagus, approximately 40 cm. from the nares. The balloon measured 12 cm. in length and 1 cm. in diameter when flattened. It was pulled over the tip of a thin plastic tubing and cemented to the tubing at its base to make the balloon air-tight. Multiple small holes in the tubing itself insured the transmission of the pressure within the balloon to the lumen of the plastic tubing. After placement of the balloon in the esophagus, it was completely evacuated and then 1 ml. of air was introduced into the balloon to permit determination of changes in pressure. Connection of the plastic tubing to a strain-gage pressure transducer of appropriate sensitivity with amplifying and recording equipment permitted continuous monitoring of the intraesophageal pressure. In the instance in which measurement of intraesophageal pressure and air flow velocity at the mouth were made, an intraesophageal balloon was introduced immediately before administration of racemic epinephrine; it was withdrawn before the post epinephrine cardiac output was determined.

Vascular pressure curves were recorded simultaneously through a cardiac catheter and an indwelling arterial needle. In all cases but 4, use of a double-lumen catheter permitted simultaneous recording of pulmonary artery and right ventricular pressure, or pulmonary artery and pulmonary wedge pressure. Strain-gage pressure transducers with appropriate amplifying and electronic recording apparatus* were used. The zero reference point for pressure measurement was the midchest at the level of the angle of Louis. The vascular pressures reported represent average values (systolic and diastolic) for 2 consecutive respiratory cycles. Pulmonary arterial wedge pressures were obtained by advancing the catheter into an arterial branch as far as possible with deep inspiration. Since it was not always possible to obtain blood samples from the tip of the catheter in this wedged position, the evaluation of the adequacy of the tracing as a record of wedge pressure was chiefly based upon a consideration of the character of the pulse pressure curves and the fluoroscopic location of the catheter tip. The catheter tip was usually left in the wedged position for 10 to 15 minutes without apparent untoward effects. Systemic and pulmonary vascular resistance indices were calculated in the manner of Gorlin et al.[3] with the assumption of mean pulmonary wedge pressure to be equivalent to mean pulmonary venous pressure.

In evaluating the effects of racemic epinephrine administration, a change of 5 mm. Hg or more in the pulmonary artery pressure, or 3 mm. Hg or more in right ventricular diastolic and pulmonary wedge pressures were considered to be significant. Changes in cardiac output greater than 15 per cent of control values were considered significant. Only changes in arterial carbon

*Research recorder, Electronics for Medicine, Inc., White Plains, N.Y.

TABLE 3.—*Effects of Racemic Epinephrine Inhalation on Ventilatory Functions, Oxygen Uptake, and Arterial Blood in Normal and Emphysematous Subjects*

| Subject | Status | $V_E/M^2$ | f | $V_T$ | $R_E$ | $V_{O_2}/M^2$ | $V_{DCO_2}$ | $pH_a$ | Arterial blood $S_{aO_2}$ | Arterial blood $P_{aCO_2}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Normal subjects | | | | | | | | | | |
| J.M. | Rest | 4.19 | 9.3 | 735 | 0.77 | 162 | 32 | 7.38 | 95 | 43 |
| | p epinephrine | 5.12 | 10.3 | 809 | 0.75 | 183 | 38 | 7.36 | 96 | 43 |
| R.M. | Rest | 4.68 | 29 | 272 | 0.74 | 135 | 27 | 7.41 | 96 | 36 |
| | p epinephrine | 4.88 | 28 | 290 | 0.59 | 154 | 34 | 7.36 | 95 | 35.5 |
| H.W. | Rest | 5.05 | 16.3 | 480 | 0.78 | 163 | 39 | 7.39 | 96 | 45 |
| | p epinephrine | 5.76 | 15.7 | 570 | 0.76 | 200 | 34 | 7.38 | 96 | 41 |
| W.R. | Rest | 4.09 | 12 | 561 | 0.75 | 142 | 33 | 7.40 | 102 | 40 |
| | p epinephrine | 5.06 | 13 | 642 | 0.75 | 154 | 41 | 7.40 | 95 | 39 |
| F.D. | Rest | 4.71 | 25 | 365 | 0.72 | 159 | 39 | 7.37 | 95 | 47 |
| | p epinephrine | 9.01 | 32 | 546 | 0.85 | 209 | 37 | 7.45 | 100 | 33 |
| Emphysematous subjects | | | | | | | | | | |
| E.S. | Rest | 6.47 | 16.7 | 620 | 0.89 | 162 | 34 | 7.47 | 93 | 34 |
| | p epinephrine | 5.72 | 14 | 654 | 0.78 | 155 | 37 | 7.48 | 93 | 34 |
| J.K. | Rest | 5.56 | 15.3 | 613 | 0.76 | 172 | 44 | 7.43 | 91 | 43 |
| | p epinephrine | 5.74 | 15.3 | 638 | 0.75 | 171 | 43 | 7.45 | 92 | 40 |
| V.G. | Rest | 4.16 | 20 | 395 | 0.72 | 135 | 35 | 7.45 | 93 | 35.5 |
| | p epinephrine | 5.44 | 24 | 430 | 0.74 | 158 | 36 | 7.48 | 93 | 31 |
| R.G. | Rest | 6.81 | 28 | 340 | 0.76 | 167 | 46 | 7.36 | 92 | 45 |
| | p epinephrine | 7.14 | 28 | 357 | 0.72 | 185 | 44 | 7.37 | 91 | 41 |
| P.M. | Rest | 3.31 | 29 | 184 | 0.69 | — | 43 | 7.33 | 75 | 70 |
| | p epinephrine | 8.11 | 37 | 484 | 0.72 | 234 | 58 | 7.37 | 75 | 61 |
| C.D. | Rest | 4.54 | 13 | 604 | 0.81 | 136 | 55 | 7.36 | 83 | 59 |
| | p epinephrine | 5.77 | 12.7 | 786 | 0.91 | 157 | 50 | 7.38 | 84 | 50 |
| G.A. | Rest | 4.70 | 18.3 | 450 | 0.77 | 144 | 51 | 7.33 | 92 | 58 |
| | p epinephrine | 6.05 | 20 | 530 | 0.78 | 178 | 50 | 7.36 | 92 | 51 |
| C.T. | Rest | 4.35 | 17.7 | 413 | 0.77 | 117 | 50 | 7.38 | 94 | 50 |
| | p epinephrine | 5.00 | 18 | 467 | 0.76 | 130 | 52 | 7.37 | 92 | 48 |
| J.B. | Rest | 4.84 | 25 | 306 | 0.78 | 145 | 48 | 7.34 | 87 | 62 |
| | p epinephrine | 5.27 | 27.3 | 305 | 0.77 | 149 | 47 | 7.34 | 88 | 57 |
| W.R. | Rest | 6.03 | 19 | 577 | 0.78 | 209 | 45 | 7.42 | 88 | 52 |
| | p epinephrine | 8.60 | 25.3 | 618 | 0.72 | 257 | 50 | 7.42 | 79 | 46 |
| E.L. | Rest | 3.83 | 17.3 | 400 | 0.77 | 147 | 38 | 7.41 | 87 | 54 |
| | p epinephrine | 3.87 | 18.3 | 382 | 0.74 | 141 | 46 | 7.35 | 85 | 61 |

dioxide tension larger than 4 mm. Hg were considered in the significant range.

## RESULTS

The data regarding the effects of racemic epinephrine inhalation on certain ventilatory functions, on the oxygen uptake by the lung, and on arterial blood gases and pH are presented in table 3. With the notable exception of the effect on arterial carbon dioxide tension, the respiratory effects were essentially the same in both the normal and the emphysematous subjects. Pulmonary ventilation rose in all the normal subjects save 1 (R.M.), an average increase of 31 per cent, and also rose in all the emphysematous patients except 1. There was no significant change in respiratory frequency following racemic epinephrine inhalation in either group, so that the increased pulmonary ventilation was achieved chiefly by virtue of an increase in tidal volume. This rose on the average 20 per cent in the normal group, and 23 per cent in the emphysematous patients. In view of the route of administration and the varying time intervals involved, the respiratory exchange ratios showed remarkably little change following racemic epinephrine

TABLE 4.—*Effects of Racemic Epinephrine Inhalation on Circulation and Respiratory Mechanics in Normal and Emphysematous Subjects*

| Subject | Status | HR | CI | SV | $\frac{Ca_{O2}}{Cv_{O2}}$ | Brachial artery pressure | | | | Wedge pressure | Pulmonary artery pressure | | | Rt. vent. end-diast. pressure | SVRI | PVRI | PIE max. var. Cm.$H_2O$ | Dynamic compliance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | S | PP | D | M | | S | D | M | | | | | |
| Normal subjects | | | | | | | | | | | | | | | | | | |
| L.M. | Rest | 78 | 4.32 | 90 | 3.5 | 100 | 42 | 58 | 75 | 9 | 19 | 7 | 13 | 5 | 1296 | 69 | —— | —— |
| | Rest | 79 | 4.63 | 96 | 3.5 | | | | | | | | | | | | | |
| | p epinephrine | 96 | 5.72 | 97 | 3.2 | 104 | 60 | 44 | 65 | — | 26 | 15 | 22 | 6 | 908 | —— | —— | —— |
| R.M. | Rest | 62 | 3.48 | 94 | 3.9 | 113 | 41 | 72 | 88 | 3 | 18 | 6 | 10 | 4 | 2175 | 175 | 7.9 | 47 |
| | Rest | 62 | 3.20 | 87 | 4.2 | | | | | | | | | | | | | |
| | p epinephrine | 86 | 4.17 | 81 | 3.7 | 139 | 62 | 77 | 100 | 8 | 30 | 10 | 19 | 5 | 1900 | 211 | 7.5 | 50 |
| H.W. | Rest | 65 | 3.76 | 90 | 4.3 | 115 | 46 | 69 | 88 | 4 | 18 | 7 | 11 | 5 | 2046 | 164 | —— | —— |
| | Rest | 64 | 3.40 | 82 | 4.8 | | | | | | | | | | | | | |
| | p epinephrine | 87 | 5.89 | 105 | 3.4 | 144 | 76 | 68 | 95 | 9 | 32 | 14 | 21 | 9 | 1103 | 163 | —— | —— |
| W.R. | Rest | 102 | 2.90 | 47 | 4.9 | 218 | 124 | 94 | 147 | 5 | 20 | 10 | 14 | 4 | 4000 | 248 | —— | —— |
| | p epinephrine | 104 | 3.21 | 51 | 4.8 | 234 | 134 | 100 | 150 | 7 | 20 | 11 | 16 | 5 | 3690 | 224 | —— | —— |
| F.D. | Rest | 78 | 3.67 | 90 | 4.4 | 139 | 49 | 90 | 104 | 3 | 10 | 6 | 8 | 0 | 2183 | 113 | —— | —— |
| | Rest | 90 | 3.88 | 83 | 4.1 | | | | | | | | | | | | | |
| | p epinephrine | 100 | 5.10 | 98 | 4.1 | 134 | 56 | 78 | 98 | 4 | 13 | 8 | 10 | 2 | 1570 | 100 | —— | —— |
| Emphysematous subjects | | | | | | | | | | | | | | | | | | |
| Group 1 | | | | | | | | | | | | | | | | | | |
| E.S. | Rest | 90 | 3.11 | 55 | 5.2 | 150 | 78 | 72 | 95 | 5 | 13 | 6 | 10 | 4 | 2900 | 154 | —— | —— |
| | p epinephrine | 106 | 3.29 | 50 | 4.7 | 163 | 85 | 78 | 101 | — | 16 | 7 | 11 | 4 | 2405 | —— | —— | —— |
| J.K. | Rest | 98 | 3.49 | 61 | 4.8 | 118 | 47 | 71 | 89 | 3 | 24 | 13 | 19 | — | 2018 | 362 | —— | —— |
| | Rest | 95 | 3.45 | 62 | 5.0 | | | | | | | | | | | | | |
| | p epinephrine | 102 | 3.28 | 55 | 5.2 | 116 | 44 | 72 | 85 | 8 | 25 | 14 | 19 | — | 2021 | 261 | —— | —— |
| Group 2 | | | | | | | | | | | | | | | | | | |
| V.G. | Rest | 80 | 3.49 | 73 | 3.9 | 107 | 47 | 60 | 82 | 4 | 19 | 8 | 13 | 3 | 1878 | 214 | —— | —— |
| | Rest | 80 | 3.36 | 71 | 4.0 | | | | | | | | | | | | | |
| | p epinephrine | 82 | 4.64 | 95 | 3.4 | 126 | 62 | 64 | 84 | — | 32 | 13 | 21 | — | 1400 | —— | —— | —— |
| R.G. | Rest | 92 | 4.44 | 68 | 3.9 | 114 | 47 | 67 | 83 | — | 31 | 15 | 20 | 4 | 1420 | —— | 13.5 | 33 |
| | Rest | 92 | 4.40 | 67 | 3.8 | | | | | | | | | | | | | |
| | p epinephrine | 101 | 5.60 | 78 | 3.3 | 120 | 53 | 67 | 86 | — | 41 | 20 | 29 | 4 | 1260 | —— | 10.2 | 48 |
| Group 3 | | | | | | | | | | | | | | | | | | |
| P.M. | Rest | 113 | —— | —— | —— | 105 | 44 | 61 | 80 | 2 | 25 | 15 | 22 | 3 | —— | —— | —— | —— |
| | Rest | 116 | —— | —— | —— | | | | | | | | | | | | | |
| | p epinephrine | 124 | 5.58 | 72 | 4.2 | 103 | 47 | 56 | 71 | 1 | 31 | 21 | 27 | — | 1018 | 372 | —— | —— |
| C.D. | Rest | 94 | 3.49 | 64 | 4.2 | 94 | 40 | 54 | 69 | 2 | 26 | 13 | 19 | 2 | 1671 | 413 | —— | —— |
| | Rest | 96 | 3.30 | 59 | 4.1 | | | | | | | | | | | | | |
| | p epinephrine | 106 | 5.05 | 83 | 3.1 | 103 | 42 | 61 | 77 | 3 | 33 | 14 | 22 | 2 | 1220 | 301 | —— | —— |
| G.A. | Rest | 86 | 3.10 | 63 | 4.9 | 163 | 74 | 89 | 129 | 6 | 32 | 22 | 26 | 5 | 3411 | 533 | 19.8 | 30 |
| | Rest | 84 | 3.00 | 62 | 4.8 | | | | | | | | | | | | | |
| | p epinephrine | 92 | 4.14 | 79 | 4.3 | 196 | 94 | 102 | 143 | 10 | 41 | 24 | 32 | 8 | 2670 | 425 | 17.8 | 42 |
| T. | Rest | 74 | 1.77 | 40 | 5.3 | 113 | 39 | 74 | 86 | 9 | 23 | 12 | 16 | — | 3070 | 269 | 11.5 | 49 |
| | Rest | 70 | 2.11 | 51 | 5.5 | | | | | | | | | | | | | |
| | p epinephrine | 76 | 2.95 | 65 | 4.4 | 110 | 38 | 72 | 91 | 8 | 27 | 14 | 19 | — | 2332 | 298 | 11.0 | 86 |
| B. | Rest | 98 | 2.87 | 46 | 4.7 | 98 | 31 | 67 | 79 | 9 | 35 | 22 | 28 | 3 | 1885 | 454 | —— | —— |
| | Rest | 100 | 3.22 | 51 | 4.5 | | | | | | | | | | | | | |
| | p epinephrine | 100 | 3.17 | 50 | 4.7 | 99 | 32 | 67 | 81 | 10 | 42 | 22 | 30 | — | 1965 | 505 | —— | —— |
| V.R. | Rest | 85 | 3.97 | 85 | 4.5 | 139 | 100 | 39 | 62 | 6 | 34 | 17 | 21 | 10 | 1399 | 366 | 11.9 | 80 |
| | Rest | 83 | 3.26 | 72 | 6.4 | | | | | | | | | | | | | |
| | p epinephrine | 101 | 5.84 | 105 | 4.4 | 154 | 108 | 46 | 77 | 12 | 44 | 23 | 29 | 11 | 987 | 233 | 13.0 | 101 |
| L. | Rest | 105 | 3.01 | 52 | 5.0 | 132 | 49 | 83 | 102 | 2 | 26 | 15 | 20 | 1 | 2662 | 470 | —— | —— |
| | Rest | 108 | 3.06 | 51 | 4.8 | | | | | | | | | | | | | |
| | p epinephrine | 108 | 3.13 | 52 | 4.5 | 120 | 47 | 73 | 96 | 2 | 26 | 14 | 19 | 2 | 2453 | 459 | —— | —— |

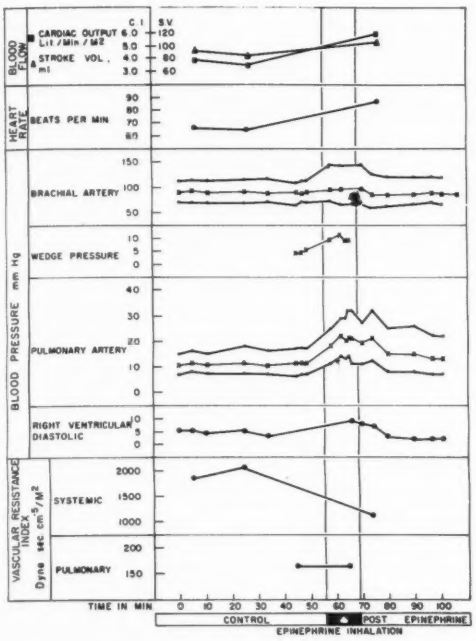
TABLE 5.—*Effects of Racemic Epinephrine Inhalation on Pressure Pulses in Brachial Artery and Right Ventricle in Normal Subjects*

| Subject | Status | Right ventricle | | Brachial artery | | Configuration brachial artery pressure curve p epinephrine |
|---|---|---|---|---|---|---|
| | | Duration interval QRS to onset contraction (sec.) | Duration mech. systole (sec.) | Duration interval QRS to end of diastole (sec.) | Duration systolic pressure pulse (sec.) | |
| J.M. | Rest | 0.05 | 0.44 | 0.16 | 0.28 | Characteristic change |
| | p epinephrine | 0.05 | 0.40 | 0.14 | 0.28 | |
| R.M. | Rest | 0.06 | 0.47 | 0.16 | 0.32 | Slight change |
| | p epinephrine | 0.04 | 0.44 | 0.13 | 0.32 | |
| H.W. | Rest | 0.04 | 0.48 | 0.16 | 0.28 | Characteristic change |
| | p epinephrine | 0.04 | 0.40 | 0.12 | 0.28 | |
| W.R. | Rest | 0.05 | 0.39 | 0.13 | 0.26 | Characteristic change |
| | p epinephrine | 0.04 | 0.32 | 0.12 | 0.26 | |
| F.D. | Rest | 0.06 | 0.38 | 0.18 | 0.24 | Characteristic change |
| | p epinephrine | 0.05 | 0.36 | 0.14 | 0.24 | |
| Average values | Rest | 0.052 | 0.432 | 0.158 | 0.276 | |
| | p epinephrine | 0.044 | 0.384 | 0.130 | 0.276 | |

administration. The mean values for respiratory exchange ratio before and after racemic epinephrine were 0.753 and 0.740 respectively in the normal group, and 0.774 and 0.765 respectively in the emphysematous patients. There was an increase in oxygen uptake by the lung in both groups. Neither group showed any significant change in respiratory dead space following the drug. In the normal group there was no consistent change in arterial blood pH, oxygen saturation, or carbon dioxide tension following epinephrine except in 1 case (F.D.), where the reduction in carbon dioxide tension was probably associated with some hyperventilation on a psychic basis. In the emphysematous patients, there was no consistent change in arterial blood pH following administration of the drug, nor was there any change in oxygen saturation, the average values being 89 and 88 per cent before and after the drug respectively. However, the arterial carbon dioxide tension fell in 6 of the emphysematous subjects.

All of the emphysematous patients except 2 showed increases in vital capacity or maximum breathing capacity or both, following inhalation of racemic epinephrine.

In table 4 are presented the data relative to the effects of racemic epinephrine inhalation on the circulation and on certain aspects of respiratory mechanics. The effects on blood flow and vascular pressures in the systemic and pulmonary circulations were similar in both the normal and emphysematous groups. However, there were distinct differences in response to the drug in the 2 groups with reference to the effect upon pulmonary vascular resistance and upon the dynamic compliance of the lung. Although there was no change in cardiac output in 4 of the patients with emphysema, all of the other subjects studied showed an increase in cardiac output that averaged about 30 per cent. This



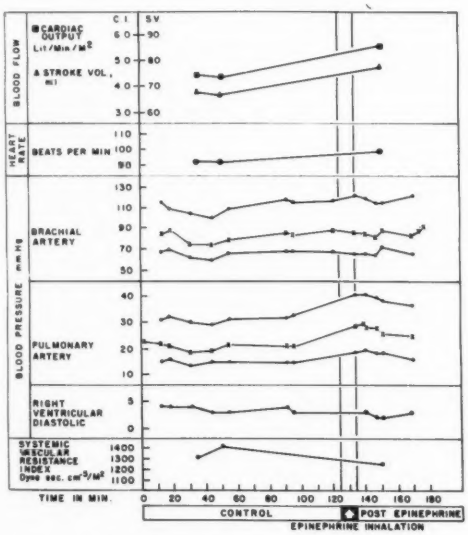




FIG. 1 *Top.* Hemodynamic response to racemic epinephrine inhalation in a normal subject. Increases in cardiac output, stroke volume, and heart rate are accompanied by rises in pulmonary wedge, pulmonary arterial, and right ventricular diastolic pressures. Calculated pulmonary vascular resistance is unchanged. The fall in systemic vascular resistance is associated with widening of systemic arterial pulse pressure.

FIG. 2 *Bottom.* Hemodynamic response to racemic epinephrine inhalation in an emphysematous subject. In this case increases in cardiac output, stroke volume, and heart rate are accompanied by a modest rise in pulmonary arterial pressure. Little change in systemic arterial pressure or calculated systemic vascular resistance occurs. Right ventricular diastolic pressure is unchanged.

was largely accomplished by virtue of an increase in heart rate that occurred in all subjects except 2, but there was a definite tendency to increase in the stroke volume, particularly in the emphysematous subjects. The stroke volume remained the same or was slightly increased in all subjects. Arteriovenous difference in oxygen content fell somewhat in all cases but 2. In the emphysematous patients there was little or no change in systolic, diastolic, or mean pressures in the systemic artery. The normal subjects showed no consistent change in mean systemic arterial pressure, but there was a definite tendency to increase in pulse pressure. In both the normal and emphysematous groups, there was a distinct tendency for pulmonary artery pulse pressures and mean pressures to rise following epinephrine inhalation. The pulmonary venous pressure as indicated by the pulmonary arterial wedge pressure, and the right ventricular diastolic pressure to a lesser extent rose somewhat in both groups. The systemic vascular resistance fell in all the normal subjects and in all the emphysematous patients but 2. On the other hand, calculated pulmonary vascular resistance, which showed no change in the normal subjects, fell in 3 out of 6 cases among the emphysematous patients. Two of these 3 patients had moderately advanced emphysema, falling into the group 3 category and the third patient had long-standing asthma and fell into the category of group 1 emphysema (J.K.). Hemodynamic data secured before and after racemic epinephrine inhalation in a normal and in an emphysematous subject are shown in figures 1 and 2 respectively.

In emphysematous patients, the maximum

TABLE 6.—*Effects of Racemic Epinephrine Inhalation on Pressure Pulses in Brachial Artery and Right Ventricle in Emphysematous Subjects*

| Subject | Status | Right ventricle | | Brachial artery | | Configuration brachial artery pressure curve p epinephrine |
|---|---|---|---|---|---|---|
| | | Duration interval QRS to onset contraction (sec.) | Duration mech. systole (sec.) | Duration interval QRS to end of diastole (sec.) | Duration systolic pressure pulse (sec.) | |
| E.S. | Rest | 0.06 | 0.33 | 0.16 | 0.34 | Characteristic change |
| | p epinephrine | 0.05 | 0.29 | 0.15 | 0.24 | |
| J.K. | Rest | | | 0.20 | 0.24 | No change |
| | p epinephrine | | | 0.18 | 0.24 | |
| V.G. | Rest | | | 0.16 | 0.30 | Characteristic change |
| | p epinephrine | | | 0.14 | 0.30 | |
| R.G. | Rest | 0.04 | 0.43 | 0.16 | 0.28 | Characteristic change |
| | p epinephrine | 0.04 | 0.36 | 0.14 | 0.28 | |
| P.M. | Rest | | | 0.16 | 0.26 | Very slight change |
| | p epinephrine | | | 0.14 | 0.25 | |
| C.D. | Rest | 0.06 | 0.36 | 0.15 | 0.26 | Characteristic change |
| | p epinephrine | 0.06 | 0.36 | 0.15 | 0.26 | |
| G.A. | Rest | 0.05 | 0.44 | 0.16 | 0.28 | No change |
| | p epinephrine | 0.05 | | | | |
| C.T. | Rest | | | 0.20 | 0.32 | No change |
| | p epinephrine | | | | 0.32 | |
| J.B. | Rest | | | 0.16 | 0.24 | No change |
| | p epinephrine | | | 0.16 | 0.24 | |
| W.R. | Rest | 0.06 | 0.46 | 0.16 | 0.24 | Moderate change |
| | p epinephrine | 0.06 | 0.36 | 0.16 | 0.24 | |
| E.L. | Rest | 0.05 | 0.36 | 0.14 | 0.22 | Characteristic change |
| | p epinephrine | 0.04 | 0.36 | 0.14 | 0.22 | |
| Average values | Rest | 0.053 | 0.388 | 0.161 | 0.262 | |
| | p epinephrine | 0.050 | 0.346 | 0.150 | 0.251 | |

variation in intrathoracic pressure as indicated by changes in intraesophageal pressure showed little or no change following epinephrine inhalation. However, there was some increase in the apparent or dynamic compli ance of the lung in all cases in which it wa measured in the emphysematous group. Dy namic compliance was determined durin

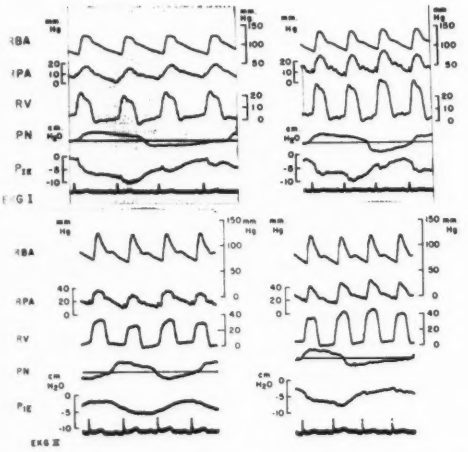


FIG. 3 *Top.* Pulse pressure curves recorded during 1 respiratory cycle before (*left*) and after (*right*) racemic epinephrine inhalation in a normal subject. In order from top to bottom are shown right brachial artery (*RBA*), right pulmonary artery (*RPA*), and right ventricle (*RV*). Below are shown an uncalibrated pneumotachographic tracing (*PN*) of airflow velocity at the mouth in which the horizontal line represents zero flow with inspiration above and expiration below, a continuous recording of intraesophageal pressure ($P_{IE}$) in centimeters of water, and electrocardiographic standard lead I (*EKG 1*). Time lines are 0.04 second. Note the sharper systolic peak of the brachial artery pressure curve after epinephrine, with greater prominence of the dicrotic notch and slight increase in pulse pressure. In this case similar changes are also seen in the configuration of the pulmonary arterial pressure curve following epinephrine. Systolic pressure rises in the pulmonary artery and right ventricle after epinephrine, and the duration of the systolic pressure rise in the ventricle is shortened.

FIG. 4 *Bottom.* Pulse pressure curves recorded during 1 respiratory cycle before (*left*) and after (*right*) racemic epinephrine inhalation in an emphysematous subject. Format of the recording is identical to that in figure 3 except that electrocardiographic standard lead II (*EKG 2*) was used. Changes in configuration and magnitude of pulse pressure curves after epinephrine are similar to those demonstrated in the normal subject.

spontaneous respiration before and after administration of the drug by computing the number of milliliters change in lung volume per centimeter water transpulmonary pressure increment from end-expiration to end-inspiration.

Table 5 summarizes the effects of racemic epinephrine inhalation on pressure pulses in brachial artery and right ventricle in normal subjects. The duration of the interval from the onset of the QRS complex of the electrocardiogram to the onset of right ventricular contraction as indicated by the systolic pressure rise was the same or slightly shortened. In order to arrive at some index of the duration of right ventricular mechanical systole that might be utilized to evaluate possible drug effect, 2 points on the right ventricular pressure curve were identified, and the time interval between them was measured. The 2 points chosen were the end-diastolic point, and a point on the descending limb of the pressure curve exactly corresponding to the level of the end-diastolic pressure. The time interval between these 2 points, referred to in tables 5 and 6 as the duration of right ventricular mechanical systole, represents an arbitrary index from which only change can be evaluated. This time interval was shortened an average of 0.048 second following racemic epinephrine inhalation. In the brachial artery the duration of the interval between the onset of the QRS complex and the onset of the systolic pressure rise was shortened an average of 0.028 second after epinephrine. There was no change in the duration of the brachial systolic pressure pulse measured from its onset to the dicrotic notch. Following epinephrine there was a consistent change in the configuration of the brachial artery pressure pulse curve, characterized by a sharper rise of the ascending limb, narrowing of the systolic peak, greater prominence of the dicrotic notch, and widening of the pulse pressure usually due to an increase in systolic pressure. Some characteristic changes in the pulse pressure curves recorded before and after epinephrine in a normal and in an emphysematous subject are shown in figures 3 and 4 respectively.

Data relative to the effects of racemic epinephrine inhalation in emphysematous subjects on pressure pulses in brachial artery and right ventricle are shown in table 6. The results are essentially the same as those obtained in the normal group. However, 4 of

the emphysematous subjects failed to show any change in configuration of the brachial artery pressure pulse after the drug.

## Discussion

Our findings of increase in heart rate and stroke volume, development of pulmonary hypertension, widened systemic pulse pressure, and reduction in calculated systemic vascular resistance are essentially the same as those previously reported in normal subjects following parenteral administration of l-epinephrine in moderate dosage.[4–9] The roughly parallel increases in pulmonary ventilation and oxygen uptake observed in normal and emphysematous subjects following racemic epinephrine inhalation are presumably related to the increased metabolic rate of the body tissues, and suggest systemic absorption of the drug.

Recent studies[10, 11] have indicated that pulmonary vascular resistance is determined by the interplay of at least several factors under normal conditions, which include the absolute levels of pulmonary arterial and left atrial pressure, the amount of pulmonary vasomotor activity, and the degree of lung inflation. Increases in pulmonary arterial or left atrial pressure are accompanied by a reduction in pulmonary vascular resistance, presumably on the basis of passive vasodilatation. Utilization of a variety of lung perfusion technics in animals has led to the demonstration of a mild pulmonary vasoconstrictor action of epinephrine.[10–13] If the pulmonary wedge pressure can be considered equivalent to the pulmonary venous pressure, then a tendency to increase in left atrial pressure following racemic epinephrine inhalation has been observed in our own studies in man. Lack of change in human pulmonary vascular resistance after administering the drug seems best accounted for by a counterbalancing of the effect of a rise in left atrial and pulmonary arterial pressure rise on the one hand, against that of increased pulmonary vasomotor activity on the other. The observed increase in pulmonary arterial pressure must accompany a greater pulmonary blood flow in the face of unchanged vascular resistance, and to a lesser extent is accounted for by the rise in left atrial pressure.

The mechanisms responsible for the observed increase in right ventricular diastolic filling pressure and the presumptive increase in left ventricular diastolic and left atrial filling pressure cannot be clearly defined on the basis of the data presented here. Reduced systemic vascular resistance with greater stroke volume and cardioacceleration would lead to an increase in left ventricular diastolic filling pressure. However, increased right ventricular stroke volume and diastolic filling pressure cannot be explained on this basis. Since the over-all effects of racemic epinephrine on the systemic and pulmonary vascular beds differ so greatly, it would seem that the changes in ventricular filling pressure are related to effects of the drug upon the heart itself. A change in ventricular pressure volume relationships is suggested.

The finding of reduction in the calculated pulmonary vascular resistance in 3 of 7 emphysematous patients after racemic epinephrine inhalation was in considerable contrast to the normal. Such reduction has also been reported by Witham and Fleming[8] in 2 patients with chronic pulmonary disease. Since no change occurred in maximal intrathoracic (intraesophageal) pressure variation after racemic epinephrine, reduced pulmonary vascular resistance was not related to change in intrathoracic pressure per se, and presumably therefore, not to intra-alveolar pressure change. The possibility is suggested that the capability for vasomotor activity in the vascular bed of the emphysematous lung may be less than normal.

Since mean pulmonary artery pressure and cardiac output rose following racemic epinephrine inhalation, right ventricular work must have increased. Similarly, an increase in left ventricular work must have occurred since no fall in systemic arterial pressure accompanied the increment in cardiac output. This increase in cardiac work was well tolerated by all patients. No untoward effects were observed following the drug except de

velopment of an occasional premature ventricular contraction in a few patients. The fact that certain emphysematous patients experienced little or no effect upon the circulatory functions measured following racemic epinephrine probably indicates that they had developed some tolerance to the drug.

Arterial carbon dioxide tension, determined by the relationship between bodily carbon dioxide production and alveolar ventilation, was reduced after racemic epinephrine inhalation only in the emphysematous patients. Since the effects of the drug upon carbon dioxide production, total pulmonary ventilation, and respiratory dead space were comparable in both the normal individuals and the patients, an improvement in alveolar ventilation-perfusion relationships is suggested as the mechanism for this lowered carbon dioxide tension. That a greater efficiency of alveolar ventilation does occur in certain emphysematous subjects following racemic epinephrine inhalation is indicated by reduction in the alveolar nitrogen concentration at the end of 7 minutes of pure oxygen breathing, and improvement in the slope of the nitrogen washout curve.[14] Improvement in distribution of inspired air to the alveoli accompanying reduction in airway resistance, and increased tidal volume probably constitute the 2 chief mechanisms responsible for the greater efficiency of alveolar ventilation observed with racemic epinephrine administration. It is notable that all the patients in group 2 and 3 of this series were found to have increases in vital capacity characteristic of the response to racemic epinephrine in chronic obstructive emphysema.

Despite the absence of significant change in intrathoracic pressure variation following racemic epinephrine inhalation in the few emphysematous patients studied, the drug resulted in a favorable modification of respiratory mechanics. An increase in tidal volume was achieved with the same intrathoracic pressure change, so that an increase in the apparent or dynamic compliance of the lung occurred. The dynamic compliance in patients with obstructive emphysema is largely determined by the flow resistive characteristics of the lung and is sensitive to changes in respiratory rate.[15] An increased dynamic compliance after racemic epinephrine despite some increment in respiratory frequency might therefore be accounted for entirely on the basis of diminished flow resistance. The data permit no conclusions regarding possible change in static lung compliance.*

The change in configuration of the systemic arterial pressure pulse that characterized the response to racemic epinephrine inhalation in our cases has been reported previously with parenteral administration of epinephrine.[16] It is not a specific change, and occurs in other clinical states such as infection and hyperthyroidism where peripheral vascular resistance is reduced. Although a change in ventricular dynamics after epinephrine administration[17] may partially account for this finding, altered vascular resistance seems to be its chief determinant.

Shortening of the duration of mechanical systole in the right ventricle was a fairly consistent observation following racemic epinephrine inhalation in our series, and appeared independent of variations in heart rate, stroke volume, and calculated pulmonary vascular resistance. Shortening of the duration of right ventricular mechanical systole after epinephrine administration has been previously observed in the mammalian heart.[18, 19] Since the dynamics of left ventricular contraction are only partially reflected in the peripheral arterial pressure pulse characteristics, failure to find a change in the duration of the brachial arterial systolic pressure pulse does not rule out alteration in left ventricular dynamics as well. The left ventricular systolic ejection period in

*The term static lung compliance is used to describe the pressure volume relationships of the lung determined by measurement of transpulmonary pressure with transient interruption of airflow at varying lung volumes. The observations reported here involving measurement of transpulmonary pressure during spontaneous respiration at lung volumes corresponding to the end-expiratory and end-inspiratory positions (zero airflow) yielded the values designated for dynamic compliance.

dogs, as indicated by analysis of aortic pressure curves, is shortened by epinephrine independent of changes in peripheral vascular resistance, heart rate, filling pressure, and stroke volume.[20, 21] It seems reasonable to conclude that the dynamics of ventricular contraction are modified similarly on both sides of the heart as a result of a direct effect on myocardial function by epinephrine.

## Summary and Conclusions

The effects of racemic epinephrine inhalation on certain cardiopulmonary functions have been studied in 5 normal subjects and in 11 patients with chronic pulmonary emphysema in order to compare the observed reactions with those known to occur following parenteral administration of l-epinephrine and to compare the drug responses in normal and in emphysematous subjects.

Comparable increases in pulmonary ventilation and oxygen uptake were observed in both normal and emphysematous subjects following the drug. Little change in arterial blood gases or pH occurred, except for a reduction in arterial carbon dioxide tension in the emphysematous group. In the absence of a change in respiratory dead space, this reduction has been attributed to an improvement in alveolar ventilation-perfusion relationships.

The effects of racemic epinephrine inhalation on blood flow and vascular pressures in the systemic and pulmonary circulations were similar in both the normal and emphysematous groups. Increases in heart rate and stroke volume resulted in higher cardiac output. Mean systemic blood pressure remained the same, and thus calculated systemic vascular resistance fell. Pulse pressure and mean pressure in the pulmonary artery rose, while both pulmonary wedge pressure and right ventricular diastolic pressure tended to increase. The calculated pulmonary vascular resistance was unchanged in the normal group, but fell in 3 of the 7 emphysematous subjects in which it was measured. Mechanisms accounting for the findings relative to calculated pulmonary vascular resistance and ventricular diastolic pressures are discussed.

The changes in brachial artery pressure pulse contour and in certain cardiac electromechanical events after racemic epinephrine inhalation were similar in the normal and emphysematous subjects. Change in the brachial artery pressure pulse contour was characterized by a sharper rise of the ascending limb, narrowing of the systolic peak, greater prominence of the dicrotic notch, and widening of the pulse pressure, usually due to a increase in systolic pressure. The duration of the interval between the onset of the QRS complex of the electrocardiogram and the onset of the systolic pressure rise in the brachial artery was shortened. The interval between the onset of the QRS complex and the onset of right ventricular contraction as indicated by the systolic pressure rise was also shortened. The duration of right ventricular mechanical systole was reduced.

Favorable modification of respiratory mechanics occurred after racemic epinephrine inhalation in the emphysematous subjects, as evidenced by increases in dynamic lung compliance, vital capacity, and maximum breathing capacity.

## Acknowledgment

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## Summario in Interlingua

Le effectos del inhalation de epinephrina racemic super certe functiones cardiopulmonar esseva studiate in 5 subjectos normal e in 11 patientes con chronic emphysema pulmonar, con le objectivo de comparar le resultante reactiones con le reactiones que occurre cognoscitemente post le administration parenteral de l-epinephrina e etiam de comparar le resultante reactiones in subjectos normal e in subjectos emphysematose.

Augmentos comparabile de ventilation pulmonar e del acceptation de oxygeno esseva observate post le administration del droga in subjectos normal e in subjectos emphysematose. Occurreva pauc alteration del gases e

del pH in le sanguine arterial, excepte que un reduction esseva notate in le tension arterial de $CO_2$ in le gruppo emphysematose. In le absentia de un alteration del spatio morte respiratori, iste reduction esseva attribuite a un melioration in le relationes inter ventilation e perfusion alveolar.

Le effectos del inhalation de epinephrina racemic super le fluxo de sanguine e super le pressiones vascular in le circulationes major e minor esseva simile in le gruppo normal e le gruppo emphysematose. Augmentos del frequentia cardiac e del volumine, per ulso resultava in un plus alte rendimento cardiac. Le valor medie del pression de sanguine systemic remaneva le mesme, e assi le calculate resistentia del vasos systemic se reduceva. Le pression del pulso e le pression medie in le arteria pulmonar montava, durante que le pression pulmonar a cuneo e etiam le pression diastolic dextro-ventricular monstrava le tendentia a augmentar se. Le calculate resistentia pulmono-vascular remaneva inalterate in le gruppo normal sed descendeva in 3 del 7 subjectos emphysematose in qui illo esseva mesurate. Es discutite le mechanismos que pote servir a explicar le constationes relative al calculate resistentia pulmono-vascular e al pressiones diastolic ventricular.

Alterationes in le profilo del pulso de pression in le arteria brachial e etiam alterationes in certe evenimentos electromechanic del corde esseva simile post le inhalation de epinephrina racemic in subjectos normal e in subjectos emphysematose. Alterationes in le profilo del pulso de pression in le arteria brachial esseva characterisate per un plus acute ascendita, un restriction del culmine systolic, un accentuate prominentia del incision dicrotic, e un allargamento del pression de pulso, usualmente como effecto de un augmento del pression systolic. Occurreva un abbreviation del intervallo inter le declaration del complexo QRS in le electrocardiogramma e le declaration del augmento de pression systolic in le arteria brachial. Esseva etiam abbreviate le intervallo inter le declaration del complexo QRS e le declaration del contraction extro-ventricular manifeste in le augmento del pression systolic. Le duration del systole mechanic dextro-ventricular esseva reducite.

Un modification favorabile del mechanica respiratori occurreva in le subjectos emphysematose post le inhalation de epinephrina racemic, manifeste in augmentos del dynamic resilientia pulmonar, del capacitate vital, e del maximal capacitate respiratori.

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The rate of excretion of a water load was measured at 20-minute intervals for a 2½-hour period before and after the administration of 75 mg. of cortisone. This test was performed in a group of patients with cardiac failure, in 14 patients with chronic disease, and in normal control subjects. The maximum rate of urine excretion, the shape of the excretion curve, and the percentage of water excreted were evaluated. In cardiac patients the excretion of water was delayed and reduced below that of controls. Following cortisone, a 33 to 225 per cent increase in the excretion of the water load was found in those with milder degrees of heart failure. In severe cases, no changes were induced by cortisone. The excretion curves of patients with chronic diseases were similar to those observed in patients with cardiac disease. A significant increase in water excretion after cortisone occurred in only 3 of 12 instances. The findings lend support to the concept that a state of functional hypoadrenocorticism may exist in some cases of cardiac decompensation and chronic disease. Suppression of antidiuretic hormone production by cortisone may play a role in the diuretic response observed.

Shuman

# Pulse Pressure Response to a Standard Exercise Stress

*By* G. H. Heidorn, M.D., M.S.

The response of pulse pressure to a standard exercise stress was utilized as the basis for an exercise tolerance test measuring left ventricular efficiency. Clinically normal individuals and asymptomatic individuals who had had a myocardial infarction were studied. Significant differences were noted between these groups. A phenomenon described as a "lag in response" was detected in many subjects with coronary artery disease. This may be a reflection of the delay in oxygen use and in other metabolic activities demonstrated by diseased myocardial tissue after an exercise stress.

THERE is a clinical need for an objective, reliable, and easily performed functional test that measures left ventricular efficiency. The purpose of this report is to present initial observations on the response of pulse pressure to a standard exercise stress in apparently normal individuals and in those who had had a myocardial infarction. Pulse pressure response shows promise of being a sufficiently sensitive index to warrant its use in the clinical evaluation of left ventricular efficiency.

## Methods and Materials

One hundred and two men older than 40 years were studied. They included 50 apparently normal individuals (average age 50.2 years), 22 who had an anterior myocardial infarction 6 months to 9 years before this study was undertaken (average age 56.8 years), and 30 individuals who had a posterior myocardial infarction 3 months to 10 years preceding this study (average age 54.9 years). The "normal" individuals were asymptomatic, had no major illnesses or surgery in the past, were receiving no medication, had a normal physical examination, and a normal 12-lead electrocardiogram. There were no cardiac murmurs of any type upon auscultation; no more than minimal retinal arteriolosclerosis was detected; and a random blood pressure was below 140/90. Subjects who had a prior myocardial infarction were likewise *asymptomatic* at the time of the study, had the characteristic electrocardiographic evidences of a myocardial infarction either primarily anterior or primarily posterior in location, and were in full-time employment.

The procedure of the exercise tolerance test was as follows: A complete history and physical examination were performed, and a standard 12-lead electrocardiogram was obtained. A 15-minute rest period in the supine position followed. If apprehension was apparent, the rest period was prolonged until apprehension disappeared. If it persisted, the subject was eliminated from the study. Brachial artery blood pressure was recorded at rest in the supine position by a mercury sphygmomanometer. The disappearance of Korotkoff sounds was used as the diastolic end-point. The subject then exercised over the Master 2-step apparatus. The number of trips was based on his age and weight.[1, 2] A single Master exercise rather than a double test was preferred. Blood pressure, again in the supine position, was recorded immediately after exercise, between ½ to 1 minute, and 2 and 4 minutes after exercise. Periods up to 10 minutes after exercise were initially used, but did not appear to offer additional information. Radial artery pulse rates were also recorded at these intervals.

The relative safety of the single Master exercise in patients who had had a myocardial infarction is demonstrated by the fact that no adverse reactions (including angina pectoris) were observed during 89 exercise periods in 52 patients with coronary artery disease. Larger numbers of patients have been exercised in other reports without adverse reactions.[3]

Results were recorded as absolute rise in pulse pressure and as per cent rise in pulse pressure (as compared to resting values) immediately following exercise. True work per beat of the left ventricle in moving blood within the aorta was calculated according to the formula published by Starr.[4]

True work (Gm.M.) = 0.54 + 68.4 pulse pressure (mm. Hg) age (years).

## Results

Pulse pressure invariably rose immediately after exercise in apparently normal individ-

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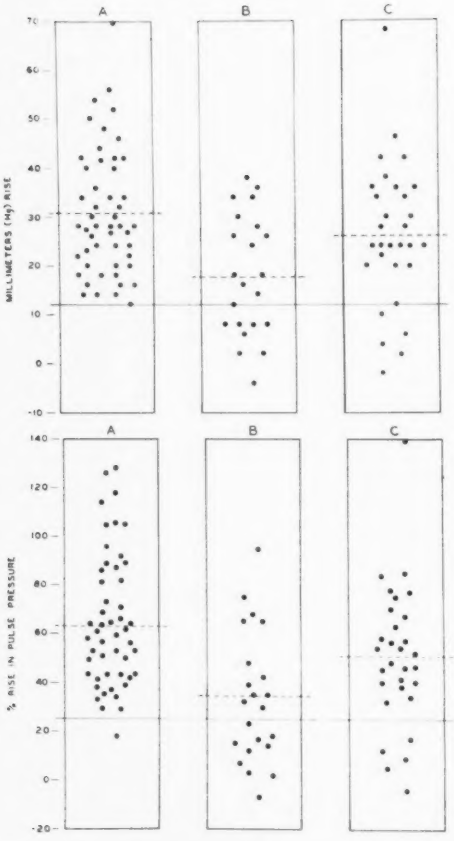


FIG. 1 *Top.* The individual response of pulse pressure in mm. Hg immediately after the completion of a standard, single Master exercise. *A*, normal controls; *B*, the anterior myocardial infarction group; *C*, the posterior myocardial infarction group. Results below the *solid continuous line* are arbitrarily selected as abnormal. *Dotted line*, average value for each group.

FIG. 2 *Bottom.* The individual per cent rise of pulse pressure immediately after exercise as compared to the resting value. *A*, normal controls; *B*, the anterior myocardial infarction group; *C*, the posterior myocardial infarction group. Values below the *solid continuous line* are arbitrarily selected as abnormal. *Dotted line*, average value for each group.

uals, and, except on 2 occasions, in those who had had a myocardial infarction. However, the magnitude of this rise varied among the 3 groups (figs. 1 and 2). Normal subjects older than 40 years averaged a 31 mm. Hg (range 12 mm. to 72 mm. Hg) rise in pulse

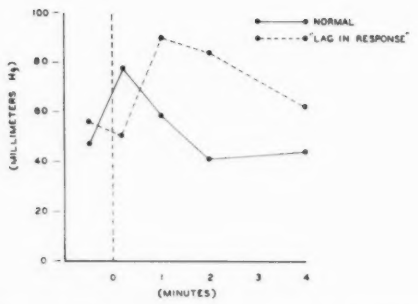


FIG. 3. Two representative individuals illustrating the "lag in response" phenomenon encountered in the myocardial infarction groups. *Vertical dotted line at O*, completion of exercise. Values preceding this line are resting values.

pressure immediately after exercise, or a 63 per cent (range 18 to 128 per cent) rise in pulse pressure when compared to resting values. Individuals with a prior *posterior* myocardial infarction averaged a 26 mm. Hg (range −2 mm. to 68 mm. Hg), or, a 51 per cent (range −4 to 142 per cent) rise in pulse pressure. Those who had a prior *anterior* myocardial infarction averaged only an 18 mm. Hg (range −4 mm. to 38 mm. Hg), or, a 34 per cent (range −7 to 95 per cent) rise in pulse pressure immediately following exercise. The group differences are portrayed in a more apparent fashion in figures 1 and 2.

If rise in pulse pressure of less than 12 mm. Hg is arbitrarily selected as an abnormal response, 8 (36 per cent) of the group with anterior myocardial disease, 5 (17 per cent) of the group with posterior myocardial disease, and none of the normal group demonstrated an abnormal response. Also, if a rise in pulse pressure of less than 25 per cent immediately after exercise as compared to the resting value is arbitrarily selected as an abnormal response, 10 (45 per cent) of the anterior myocardial infarction group, 5 (17 per cent) of the posterior myocardial infarction group, and 1 of the 50 normal individuals fell below this dividing percentile. It is to be emphasized that these are arbitrarily selected standards that are subject to change as experience widens.

A "lag in response" (fig. 3) is defined a

a greater pulse pressure at 1 minute after exercise than immediately after exercise. Pulse pressure is normally greatest immediately following exercise. A "lag in response" in this study was a phenomenon characteristic of a diseased myocardium. It was observed in 8 (36 per cent) individuals with a prior anterior myocardial infarction (2 of whom had an otherwise normal result), and 10 (37 per cent) times in those with a prior posterior myocardial infarction (6 of whom had an otherwise normal result). It was not noted in apparently normal individuals. The "lag in response" phenomenon was most dramatically illustrated by 2 patients with coronary artery disease in whom the pulse pressure actually fell 4 and 7 per cent, respectively, immediately after exercise (figs. 1 and 2).

Pulsus alternans after exercise was detected in some patients by the mercury sphygmomanometer. This was recorded as an abnormal response.[5] Pulsus alternans was observed in 2 indivduals in both the anterior and posterior myocardial infarction group (3 of these 4 subjects had an otherwise normal response to the exercise stress). It was not noted in the normal group.

In summary, the following responses were arbitrarily selected as abnormal ones: a rise in pulse pressure of less than 12 mm. Hg or less than 25 per cent immediately after exercise, a "lag in response," and pulsus alternans after exercise. Usually, more than one of the above responses were observed in an individual who had an abnormal result. At least one of these abnormalities was noted in 13 (59 per cent) of those with anterior myocardial disease, 13 (43 per cent) of those with posterior myocardial disease, and in 1 apparently normal subject who had an 18 per cent rise in pulse pressure, but, had an otherwise normal response.

It is of interest in the light of this study to evaluate some of the indices that have been used as a guide to cardiac function in the past. The older criteria considered a normal response to be a return of systolic and diastolic blood pressure and of pulse rate to within 10 "points" of the resting value 2 minutes after a standard single Master exercise.[1, 2] These criteria have been reported to be of insufficient sensitivity.[3] This impression is confirmed by this study. Pulse rate did not return to within 10 beats per minute of the resting rate in 5 patients with an anterior myocardial infarction, 5 patients with a posterior myocardial infarction, but also in 6 normal subjects. Likewise, the return of pulse pressure to within 10 mm. Hg of the resting value within 2 minutes was an insensitive index. An "abnormal" result based on this criterion was present in 17 normal individuals, as well as in 16 patients with posterior myocardial disease and in 12 patients with anterior myocardial disease.

Normally, a fall in diastolic blood pressure is expected after exercise. However, this is not an invariable finding. Diastolic blood pressure fell after exercise in only 30 of the 50 normal subjects, 12 of 30 individuals who had posterior myocardial infarctions, and 10 of 22 individuals with anterior myocardial disease. Although diastolic blood pressure usually fell following exercise in normal subjects and usually rose in subjects with coronary artery disease, it was not a sufficiently sensitive index for use as an additional measure of response to exercise. There was no apparent correlation in the coronary artery disease group between rise in diastolic pressure and the occurrence of an otherwise abnormal or normal result.

Among other indices determined in this study were postexercise changes in true work per beat of the left ventricle in moving blood within the aorta. These data were calculated according to Starr's formula.[4] The values are not herein tabulated because changes in true work were comparable to pulse pressure changes. Interestingly, true work per beat at rest was generally alike in all 3 groups studied. Normal individuals averaged 74.1 Gm. M. per beat; the anterior infarction group averaged 65.1 Gm. M.; and the posterior infarction group averaged 67.3 Gm. M. Immediately after exercise, the normal group averaged 115.5 Gm. M. per beat; the anterior myocardial infarction group averaged 82.7 Gm. M.; and the posterior myocardial infare-

TABLE 1.—*Comparison of Pulse Pressure Responses at Varying Time Intervals in Patients with a Prior Myocardial Infarction*

| Patient no. | Time Since infarction (months) | Pulse pressure response <mm. Hg. (%)> | | Interval clinical changes |
|---|---|---|---|---|
| 1 | 3 | < 2 (5) | lag> | none |
| | 10 | 6 (9) | lag | |
| 2 | 8 | 34 (65) | | none |
| | 16 | 30 (63) | | |
| | 19 | 32 (78) | | |
| 3 | 50 | − 4 (−7) | lag | steady electrocardiographic improvement |
| | 54 | 0 (0) | lag | |
| | 59 | 10 (25) | lag | |
| 4 | 48 | 8 (17) | lag | 25 lb. weight loss and electrocardiographic improvement |
| | 60 | 20 (50) | lag | |
| 5 | 36 | 6 (12) | pulsus alternans | none |
| | 42 | 26 (65) | no pulsus alternans | |
| 6 | 10 | 38 (95) | | none |
| | 17 | 40 (100) | | |
| 7 | 6 | 16 (40) | | none |
| | 13 | 20 (43) | | |
| 8 | 3 | 2 (3) | lag | electrocardiogram returned to normal |
| | 6 | 12 (22) | lag | |
| | 12 | 12 (18) | lag | |
| 9 | 10 | 28 (48) | | 15 lb. weight reduction, improved electrocardiogram |
| | 16 | 44 (88) | | |
| | 20 | 34 (74) | | |
| 10 | 48 | 8 (14) | lag | none |
| | 53 | 10 (21) | lag | |
| | 57 | 6 (11) | lag | |
| 11 | 20 | 24 (35) | | none |
| | 24 | 44 (79) | | |
| | 27 | 36 (69) | | |
| 12 | 4 | 30 (75) | | electrocardiogram returned to normal |
| | 8 | 26 (57) | | |
| | 12 | 36 (106) | | |
| 13 | 29 | 26 (42) | lag | none |
| | 40 | 34 (53) | lag | |
| 14 | 3 | 42 (78) | no pulsus alternans | none |
| | 8 | 26 (37) | pulsus alternans | |
| 15 | 4 | 24 (39) | lag | none |
| | 6 | 36 (64) | no lag | |

tion group averaged 100.4 Gm. M. Further experience is required to determine if the absolute value of true work per beat or per minute is a more significant index of left ventricular efficiency after exercise than is the change in pulse pressure.

Pulse pressure responses in younger normal individuals are included here for completeness. The results were not added to the data contained in the body of this report in order to maintain similar average ages for all 3 groups studied. This group consisted of 20 men (average age 29.9 years) who met the criteria of normalcy as outlined for older apparently normal individuals. The younger normals averaged 32.0 mm. Hg (range 18 mm. to 60 mm. Hg), and a 67.5 per cent (range 35 to 120 per cent) rise in pulse pressure following exercise. They also averaged 118.2 Gm. M. of work per beat of the left ventricle at rest and 196.7 Gm. M. per beat immediately after exercise.

In order to lend reliability to an exercise tolerance test, the results must be reproducible in successive testings. Reproducibility of results was determined in many individuals included in the myocardial infarction groups (table 1). Generally, the response of pulse pressure to exercise is reproducible in the same individual at varying time intervals. When results are at variance, the differences can usually be explained by changes in the clinical status of the patient. However, at times no clinical explanation for differences in response was at hand (table 1, patients 5, 11, 14, and 15).

## DISCUSSION

The clinical determination of left ventricular efficiency is based chiefly upon an evaluation of symptoms. Dyspnea is of prime importance in this regard. Dyspnea, however, is a subjective symptom. Its appearance in a given individual is governed by many psychologic and physiologic factors.[6] It is not necessarily an objective measurement of the functional status of the left ventricle. Exercise tolerance tests have been utilized in an attempt to measure the status of the left ventricle in a somewhat more objective fas-

tion.[7-9] Various exercise tolerance tests including those that use the Master 2-step apparatus,[1, 2] tilt-tables,[10] and motor-driven treadmills[11, 12] have originated. The Master 2-step exercise offers the advantages of simplicity, availability, and wide experience in its use. It is a relatively brief stress that requires energy expenditures comparable to everyday life.[3] It is standardized by the age and weight of the patient. The indices that have been most widely used to measure left ventricular efficiency are a return of pulse rate and systolic and diastolic blood pressures to within 10 "points" of resting values within 2 minutes after the completion of a single Master exercise. In this study, as well as in others,[3] these indices have not proved sufficiently sensitive. Exercise tolerance tests in general have been of only limited value to the clinician.

Pulse pressure offers an advantage as an index of ventricular function that pulse rate and systolic and diastolic blood pressures do not possess. Pulse pressure has been more closely correlated with the actual work per beat of the left ventricle in moving blood within the aorta than have the other measurements.[4] The response of pulse pressure to a standardized exercise stress was, therefore, utilized as the basis for an exercise tolerance test to measure the functional efficiency of the left ventricle.

The magnitude of pulse pressure rise as measured immediately after the completion of a single Master exercise was used as the index of response. Generally, the average rise of pulse pressure was greater in apparently normal individuals than in those asymptomatic individuals who had had a myocardial infarction (figs. 1 and 2). Also, the response was poorest in those subjects who had electrocardiographic evidence of a primarily anterior myocardial infarction. Although this series is too small to derive conclusions, this difference is perhaps related to the observation that the greatest proportion of the work of systolic ejection is performed by the interventricular septum and the anterior wall of the left ventricle.

The "lag in response" phenomenon as previously described is of considerable interest. It is apparently a characteristic of diseased myocardial tissue. It was not noted in normal subjects, but was present in more than a third of those with a prior myocardial infarction. This phenomenon is very likely related to the lag in oxygen use[3, 13, 14] and to the delay in the mobilization of other metabolic activities that is exhibited by diseased myocardial muscle after an exercise stress.[15] This delay in metabolic mobilization in the acute period following stress probably results in a lessened work ability of the muscle, a deficient cardiac output, and a lessened pulse pressure response. It is important to emphasize that the "lag in response" phenomenon would not be detected if physiologic measurements are first made 2 minutes after exercise is completed as is done in previously reported tests. Measurements should be made in the immediate period following exercise.

The occurrence of pulsus alternans after exercise was interpreted as an abnormal response and was added to the other criteria.[5] Pulsus alternans after exercise was detected by the sphygmomanometer in 4 patients with coronary artery disease, but was not noted in normal subjects.

Usually more than one of these criteria that indicate an abnormal response were met in any given patient who demonstrated an abnormal result. At least one of them was filled in 59 per cent of indivduals who had a prior anterior myocardial infarction and in 43 per cent of those who had a prior posterior myocardial infarction. On only one occasion did an individual in the apparently normal group demonstrate an abnormal result. This was an isolated occurrence of a less than 25 per cent rise in pulse pressure. It is to be remembered that all of the subjects included in the group with coronary artery disease were asymptomatic. The only clinical residua of a myocardial infarction were contained in the electrocardiogram. Only an expected degree of dyspnea was experienced during exercise. It was therefore not possible to correlate pulse pressure responses with symptomatology. One might speculate that in many instances the response of pulse pressure to

exercise reveals abnormal myocardial function sooner than does the appearance of dyspnea.

Pulse pressure responses were generally reproducible upon repeat testings at varying time intervals (table 1). When the results were at variance, the differences could usually be explained by changes in clinical status such as significant weight reduction or changes in the electrocardiogram. At times, no explanation for the variations were at hand.

This exercise tolerance test has revealed a significantly greater incidence of abnormal responses in asymptomatic subjects with coronary artery disease than in a total of 70 apparently normal individuals. This fact encourages further study of this procedure. It is important in the performance of this test that pulse pressure be measured immediately and 1 minute after exercise is completed in order to detect the "lag in response" phenomenon, which seems to be a phenomenon characteristic of diseased myocardial tissue. The applications of this test would seem to be greatest as a screening procedure, as an evaluation of individuals with bundle-branch block, or in those with borderline electrocardiographic changes. Investigations in this regard are in progress.

## Summary

The response of pulse pressure to an exercise stress, standardized as to the age and weight of the individual and performed on the Master 2-step apparatus, was utilized as the basis for an exercise tolerance test. Pulse pressure was selected in preference to other physiologic indices such as pulse rate, systolic and diastolic blood pressure, etc., as it is more closely correlated with the true work per beat of the left ventricle in moving blood within the aorta.

The magnitude of pulse pressure rise as recorded immediately after the completion of the standard exercise showed considerable variation between 50 apparently normal individuals and an asymptomatic group of comparable ages composed of 22 individuals who had had an anterior myocardial infarction and 30 individuals who had had a posterior myocardial infarction.

An abnormal pulse pressure response t exercise was arbitrarily selected as follows (1) a rise in pulse pressure immediately fol lowing exercise of less than 12 mm. Hg o less than 25 per cent, (2) a "lag in re sponse," (3) or pulsus alternans after exer cise. At least one of the above criteria o abnormality was noted in 59 per cent of in dividuals who have anterior myocardial dis ease and in 43 per cent of individuals wh have posterior myocardial disease. There wa only an isolated occurrence of an abnorma result in the normal group. In general, sub jects with posterior myocardial disease per formed better in this study than did thos with anterior disease.

A "lag in response" is defined as a greater pulse pressure at 1 minute after exercise than immediately after the exercise was completed. This phenomenon was specific in this study for individuals with a prior myocardial infarction and occurred in more than a third of this group.

The use of pulse pressure response to exercise as a measure of left ventricular function shows promise of being sufficiently sensitive for practical clinical application and merits further study.

## Acknowledgment

The technical assistance of Mrs. Helen Jordan, R.N., Mr. John W. Houser, and Miss Ruth Ann Knouse is gratefully acknowledged.

## Summario in Interlingua

Le responsa del pression del pulso a stress per exercitio—standardisate con respecto al etate e al peso del subjecto e executate con le apparato bigradate de Masters—esseva usate como indice in un test del tolerantia de exercitios. Le pression del pulso esseva seligite plus tosto que altere indices physiologic—per exemplo le frequentia del pulso, le pression sanguinee systolic e diastolic, etc.—proque illo es plus directemente correlationate con le v r labor que le ventriculo sinistre executa p r pulso individual in mover le sanguine int a le aorta.

Le magnitudes del augmento in pression del pulso mesurate immediatemente post le completion de un exercitio standard variava considerabilemente inter (1) 50 apparentemente normal individuos e (2) un gruppo de individuos asymptomatic de etates comparable, includente 22 individuos que habeva habite un infarcimento antero-myocardial e 30 qui habeva habite un infarcimento postero-myocardial.

Anormalitate del responsa del pression del pulso al stress de exercitio esseva definite arbitrarimente como respondente al sequente criterios: (1) Un augmento in le pression del pulso immediatemente post le exercitio amontante a minus que 12 mm de Hg o a minus que 25 pro cento, (2) "retardo del responsa," o (3) pulso alternante post exercitio. Al minus un de iste tres criterios de anormalitate esseva notate in 59 pro cento del individuos con morbo antero-myocardial e in 43 pro cento del individuos con morbo postero-myocardial. In le gruppo normal il habeva solmente un occurrentia isolate de un resultato anormal. In general, subjectos con morbo postero-myocardial exiva melio in iste studio que subjectos con morbo antero-myocardial.

"Retardo del responsa" es definite como le occurrentia de un pression del pulso plus grande 1 minuta post le exercitio que immediatemente post su completion. Iste phenomeno esseva, in le presente studio, specific pro individuos con previe infarcimento myocardial e esseva notate in plus que un tertio de illes.

Le uso del responsa del pression del pulso a standards de exercitio como mesura del function sinistro-ventricular promitte monstrar se sufficientemente sensibile pro practic objectivos clinic. Illo merita investigationes additional.

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# Lead Field Scalar and Loop Spatial Electrocardiography

## A Preliminary Survey on Normal Adult Males and Comparison with Other Methods

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Spatial electrocardiography based on the lead field concept of McFee and Johnston appears to be theoretically more satisfactory than other systems of vectorcardiography. To determine the normal range of planar loop patterns to be expected with this technic and to compare them with those derived by previous methods, a survey of young adult males has been carried out with particular reference to the sagittal plane. The possible relationship between loop orientation and anatomic cardiac position has been investigated and a comparison made of main loop axes and the corresponding electric axes as calculated from scalar tracing areas.

SCALAR electrocardiography has, during the past 50 years, yielded a great deal of information concerning the electric phenomena accompanying cardiac activity but it has recently been suggested by Wolff, Richman and Soffe[1] and others that the clinical methods in current use have been thoroughly explored and that their usefulness is unlikely in the future to be extended to any important degree. Nevertheless, it is now generally acknowledged that study of the cardiac electric impulse as a 3-dimensional vector quantity may provide more fundamental information both to the physiologist and the clinician. Unfortunately, as in other fields, a multiplicity of technics already designed to investigate the spatial nature of the heart's electric activity indicates that no one approach has so far proved satisfactory, but a new method to be presented here and based upon the theoretical arguments of McFee and Johnston[2–4] shows promise of being superior to any previously described.

Burger and van Milaan[5–7] have pointed out on theoretical grounds, and confirmed by experiments on synthetic torsos, the errors involved in using any given orthogonal vectorcardiographic reference frame for all individuals because of variations in such factors as tissue resistivity, body contour, and anatomic position of the heart from one subject to another. In consequence of these differences the equilateral triangle of Einthoven, although a satisfactory compromise for most purposes, should in fact be modified in shape for each individual to serve as his characteristic frontal plane reference frame. It follows that the placement of electrodes at anatomically identical positions on the trunks of all persons cannot be expected to yield accurate planar projections of their spatial cardiac electric activities since, as Johnston[8] has emphasized, "Vectorcardiograms can be no more accurate or informative than are the leads employed to derive them." The lead that has been most open to criticism in the commonly used systems of vectorcardiography has been the anteroposterior or sagittal, and recently much attention has been directed to establishing a theoretically more satisfactory method for recording potentials in this plane.

McFee and Johnston[2] studied the spatial dispersion of electromotive forces in the heart and formulated a theory closely related to the "lead vector" concept of Burger and van Milaan.[5–7] They applied the reciprocity theorem of Helmholtz[9] to the problem of the heart as a source of electromotive force within a volume conductor (the thorax) by determining the electric field set up within the heart when unit current is introduced into

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any given lead. The resulting "lead field" can be visualized by analogy to the flow of water (free from turbulence and eddies) through the body from an inlet at one electrode of the bipolar lead to an outlet at the other. The field flow lines will be parallel along the straight course joining the 2 electrodes but the more lateral lines will pursue more convex courses as the stream widens away from the inlet and will converge again toward the outlet. The electric field of lead I, for example, as visualized in this manner, is shown in figure 1*A* where it is seen that the flow lines do not traverse the heart horizontally but in an upward direction toward the left shoulder. Consequently, lead I cannot be regarded as a truly horizontal lead as is depicted in the Einthoven triangle.

By similar reasoning it can be argued[3] that the sagittal leads used in the "tetrahedron" system of Conway, Cronvich, and Burch[10] and "cube" system of Grishman, Borun, and Jaffe[11] give lead fields through the heart that are grossly displaced from the true sagittal direction. Neither of these types of geometrical reference frame can, therefore, yield anything but very distorted sagittal plane projections of the cardiac electric activity.

A modification of the "cube" system recommended by Lamb and Dimond[12] utilizes a sagittal lead that, on theoretical grounds, is slightly more satisfactory, but it has not been widely accepted.

It was suggested by McFee and Johnston[4] that a corrective lead in parallel with lead I and obtained by placing electrodes on the lower thorax in the anterior axillary lines would give a lead field through the heart that was much more truly horizontal (as indicated in fig. 1*B*) and that a multi-electrode assembly placed over the precordium with a similar electrode unit directly posterior to the heart would give a perfect sagittal lead (see fig. 1*C*). We have, therefore, used this combination of leads for recording the horizontal planar projection of the cardiac instantaneous vectors together with a lead between the

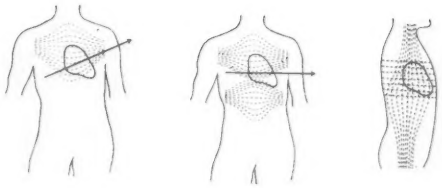

FIG. 1. Lead fields through the heart. *Left A.* Standard lead I. *Middle B.* Corrected horizontal lead for lead field technic. *Right C.* Sagittal and vertical leads for lead field technic.

right side of the neck and left leg for the frontal and sagittal planes (fig. 1*C*). The effect on the horizontal planar loop contour of the corrective thoracic lead can be seen in the lower sets of records in figure 2.

While the present work was in progress, Frank[13] described a somewhat similar attempt to produce a satisfactory sagittal lead with what he calls "an accurate, clinically practical system" of electrode placement using a combination of 7 electrodes, 5 of which are placed around the thorax, in association with complicated resistor networks. Brody[14] has, however, questioned the validity of Frank's method in certain circumstances but his criticism may not be well founded.

Some attention had initially to be given to the number of separate electrodes that should be incorporated into the multiple chest units and for this purpose a series of preliminary experiments was carried out, the results of which are shown in figure 2. Horizontal plane loops were obtained using the corrected McFee and Johnston horizontal lead with, in turn, (*a*) a standard small suction chest electrode on the precordium at position $V_3$ and a similar one directly posterior to the heart, (*b*) a standard limb electrode replacing each suction electrode, (*c*) a 5-electrode chest unit in each position and, finally, (*d*) a 16-electrode chest unit anteriorly and posteriorly. Little difference in general loop contour was observed on simply increasing the area of a single electrode as by replacing the suction type by a limb electrode. However, increasing the number of electrodes in each chest unit to 5 produced a marked change in shape

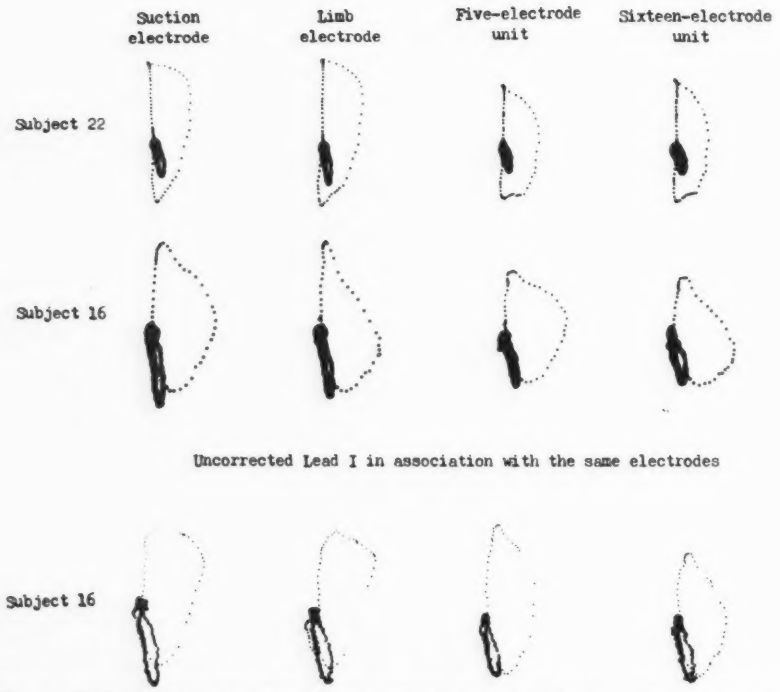


FIG. 2. Horizontal plane loops using various types of chest electrode. Corrected horizontal lead in association with electrodes anteriorly and posteriorly.

of the loops but further increasing the number to 16 had little additional effect. Consequently, we have used 5-electrode assemblies throughout the present study, but, since in practice it has been found that the 16-electrode type is more pliable and hence more easily moulded to the chest wall, that type will in future be used for adults.

Reynolds, Cordes, Willis, and Johnston[15] have also investigated the effect of varying the numbers of separate electrodes in multiple chest units commencing with grids containing 63 point electrodes but they found little difference when the number was reduced to 16 and concluded that "it may be possible to use as few as nine or even six anterior electrodes and still obtain a fairly accurate sagittal electrocardiogram." The fact that changing the area of each electrode in an assembly is not likely materially to affect the resulting loops has recently been confirmed by Brody.[14]

## METHODS

The subjects used in this study were 47 male medical students, aged between 19 and 21 years, who had no previous history of cardiac disease and showed no clinical evidence of abnormality on physical examination. All investigations were carried out with the subject respiring quietly and supine on a couch with the head-rest raised by about 20°.

By means of an Elmqvist Mingograph Type 23 direct-writing electrocardiograph, with the 2 channels accurately synchronized, the standard limb leads I-II and I-III and augmented voltage leads $aV_R$-$aV_L$ and $aV_R$-$aV_F$ were first recorded at normal paper speed (25 mm. per second) and at fast speed (100 mm. per second). The unipolar chest lead tracings ($V_{1R}$ to $V_6$) were obtained singly at 50 mm. per second.

Fast speed records were then made by placing electrodes on the body at positions judged most suitable to satisfy the requirements of the lead field theory. These positions, shown diagrammatically in figure 3, are as follows: (i) Right side of neck approximately 2 inches above the level of

the clavicle. A specially shaped convex electrode to fit the curvature of the neck and 1½ sq. in. in area was used. (ii) Left leg (standard limb electrode). (iii) On each side a compound electrode consisting of 1 limb electrode placed on the arm and another on the thorax over the eighth rib in the anterior axillary line, the 2 connected in parallel through 5 KΩ resistors to a common terminal. (iv) A multiple chest electrode on the precordium over the anatomic position of the heart and another in the corresponding position posteriorly. Each consisted of a cluster of 5 small electrodes connected in parallel through 20 KΩ resistors to a common terminal.

A diagram of this multiple chest electrode unit is given in figure 4. It was constructed from a sheet of polythene, 4½" x 4½" x ⅛", which was milled to a depth of 1/16" on one face leaving 5 "islands," each of the outer 4 being 1" x 1" and the central one 1½" x 1". To the surface of each of these islands an electrode plate of pure tin 1/32" thick was fastened and connected in series with a 20 KΩ resistor embedded in a groove milled out from the back of the polythene. The leads from the 5 small resistors were connected in parellel to a common terminal flex about 18" long. The back of the polythene sheet with its resistors and wires was covered with molten Chatterton's cement and a thin layer of rubber pressed tightly over it. When the excess cement was removed the multiple electrode unit was sufficiently pliable, when held in place by rubber straps, to conform to the curvature of the thorax.

For determination of the lead field potentials the Mingograph was fed through a selector junction box to record the scalar tracings of each of the following planes:

Frontal plane:
(X-axis) Lead A....Electrodes (iii)-(iii)
(Y-axis) Lead C....Electrodes (i)-(ii)

Horizontal plane:
(X-axis) Lead A....Electrodes (iii)-(iii)
(Y-axis) Lead B....Electrodes (iv)-(iv)

Sagittal plane:
(X-axis) Lead B....Electrodes (iv)-(iv)
(Y-axis) Lead C....Electrodes (i)-(ii)

With the electrodes in the same positions the frontal, horizontal and sagittal plane loops were then displayed in turn on the cardioscope screen and the directions of rotation of the QRS and T loops noted.

The cardioscope used was built in the laboratory and consisted of a Twentieth Century Tube (Type S B) with optically flat short persistence blue screen, run at 4KV to give a fine spot and having brightness, focus, astigmatism, aberration and spot-shift controls. Each pair of plates was supplied by a 5-stage push-pull R-C coupled amplifier having an over-all time constant of 1.5 seconds. The beam was interrupted by brightness modulation every 1/1000 second and a slow-running timebase could be switched in for visualization of the scalar patterns of either component lead.

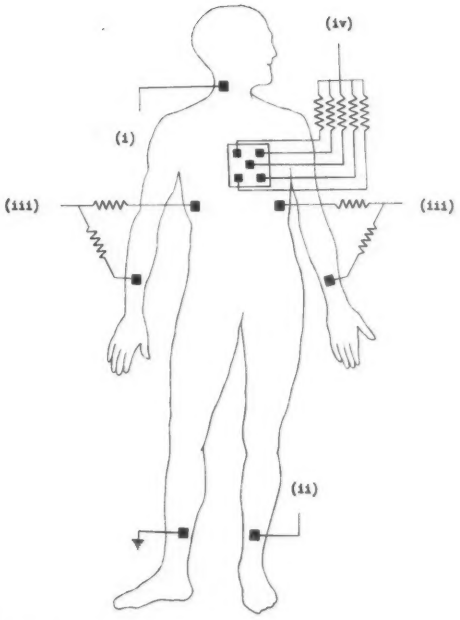


FIG. 3. Lead field technic electrode positions.

Before registration of the loops the X- and Y-plate amplifiers were balanced by injecting 1 mV pulses on to both pairs of plates simultaneously from a mechanical switch operating at 5 c.p.s. and adjusting the gain controls to give a spot response along a line of required length at an angle of 45° on the screen. Polarities from the input selector switch were arranged so as to give frontal plane loops oriented downward and to the patient's left when viewed from the front and sagittal plane loops as though the heart were viewed through the right side of the thorax.

To the front of the cardioscope was attached a Cossor camera (Model 1428) with Kodak R60 35-mm. film. Several static pictures of single loop complexes were taken and also moving-film photographs throughout several successive cardiac cycles with a film speed of 1" per second. Each record was calibrated by superimposing the deflection from a 1 mV input pulse on to the film at the commencement of each set of observations.

For comparative purposes scalar tracings at fast speed on the Mingograph and cardioscope loops resulting from the use of the Grishman

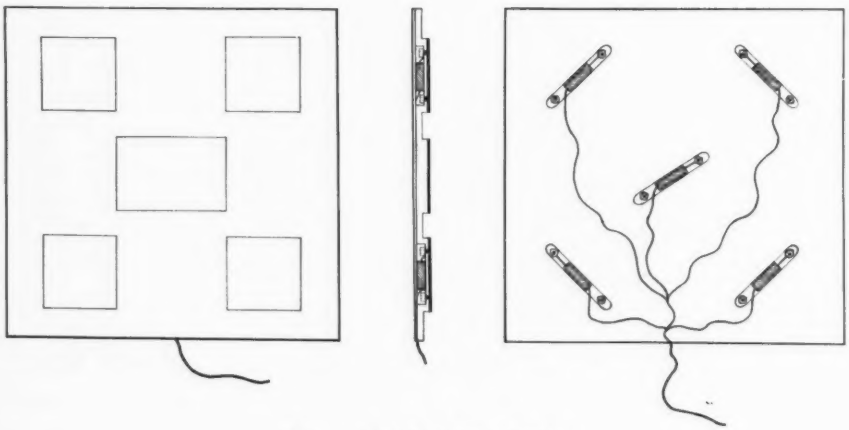

FIG. 4. Multiple chest electrode.

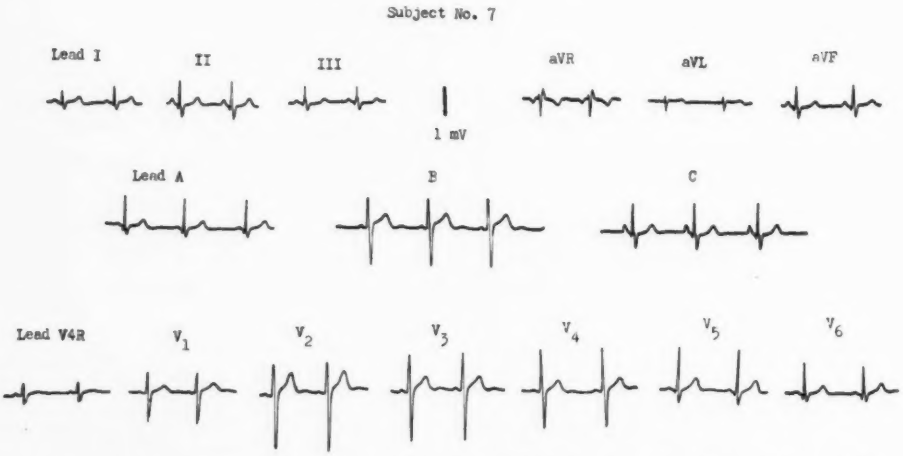


FIG. 5. Comparison of lead field scalar tracings with those of the standard limb and chest leads.

"cube" system of electrode placement were also obtained for each subject and in a few cases similar data using the "tetrahedron" and modified orthogonal (Lamb and Dimond) technics.

## RESULTS

Before the lead field scalar records were analyzed the tracings from the standard limb leads I, II, and III, the augmented voltage leads $aV_R$, and $aV_L$ and $aV_F$ together with the unipolar chest leads $V_{4R}$ to $V_6$ for each subject were carefully scrutinized and all were found to be within normal limits.

A typical set of scalar tracings obtained using the lead field system is shown in figure 5 for comparison with the conventional patterns for the same individual.

The mean values for the time intervals and durations from the scalar tracings of each of the leads A, B, and C for all 47 subjects are given in table 1. Six complete complexes in each lead from each person were measured in order to eliminate respiratory effects and the subject's average values for each interval determined. The 47 individual means were then submitted to statistical analysis to de-

TABLE 1.—*Analysis of Lead Field Scalar Tracings: Mean Time Intervals in Seconds and Ninety-Five Per Cent Probability Limits*

| | P-R interval | | QRS duration | S-T segment | T duration | T-P interval | P-P interval | Heart rate | Duration of electric activity (beginning of P to end of T) |
|---|---|---|---|---|---|---|---|---|---|
| | P duration | P-Q (R) segment | | | | | | | |
| Lead A | 0.08 (0.05-0.11) | 0.07 (0.03-0.11) | 0.08 (0.06-0.10) | 0.05 (0.00-0.10) Elevation in 9 cases | 0.24 (0.16-0.32) | 0.36 (0.14-0.58) | 0.87 (0.62-1.12) | 70 (48-92) | 0.51 (0.43-0.59) |
| Lead B | 0.09 (0.06-0.12) | 0.07 (0.03-0.11) | 0.09 (0.07-0.11) | Elevation in 46 cases | 0.27* (0.22-0.32) | 0.35 (0.13-0.57) | 0.87 (0.62-1.12) | 71 (49-93) | 0.52 (0.45-0.59) |
| Lead C | 0.09 (0.06-0.12) | 0.07 (0.03-0.11) | 0.09 (0.07-0.11) | 0.04 (0.00-0.09) Elevation in 12 cases | 0.25 (0.18-0.32) | 0.35 (0.13-0.57) | 0.88 (0.63-1.13) | 70 (48-92) | 0.53 (0.45-0.61) |

* See text.

tain the grand means quoted and their standard deviations (S.D.). The ranges given in table 1 indicate the limits set by twice the standard deviation on either side of the mean and, therefore, the values within which 95 per cent of the individual means from the population sampled may be expected to lie.

The time intervals for lead A are closely similar to those observed in the corresponding lead I and, in all leads, despite widely varying heart rates among the subjects, the duration of electric activity as measured by the interval "beginning of P to end of T" is remarkably constant.

In all subjects, except 2, the S-T segment in lead B was distinctly elevated above the isoelectric line and in 32 cases this was associated with the presence of a U wave having an average duration of 0.19 second. Segment elevations were also noted in lead A of 9 individuals and in lead C of 12, but without accompanying U waves.

Analysis of the 47 values showed that the duration of QRS was significantly longer in leads B and C than in lead A by about 13 per cent, so that the 2 leads of the sagittal plane give a truer estimate of the period of depolarization than does lead A.

Because of the elevation of the S-T segment in lead B no time value could be assigned to that segment in this particular lead and hence the times given in table 1 for the duration of T in lead B are, in fact, those from the end of S to the end of T. This period, which is assumed to be the best estimate of the time taken by repolarization, is seen to be shorter in lead B (0.27 second) than in either of the leads of the frontal plane (0.29 second), so that these are to be preferred when determining the actual duration of repolarization. From these considerations of the relative durations of QRS and (S-T) +.T in the 3 leads, it follows that the ratio of the duration of repolarization to that of depolarization will be greatest in lead A, where it is 3.6 (S.D. 0.7), and smallest in lead B (3.1, S.D. 0.4).

For the presentation of loops and vectors derived by the lead field system we have adopted the first of the "consistent" notations advocated by Helm,[16] since it is the most satisfactory and logical so far proposed (in spite of the preference of Robertson[17] for the second of Helm's alternatives) except that we have substituted the term "horizontal" for "transverse" in order to avoid possible confusion of symbols (*vide infra*). The arrangement of the axes in the three planes of space and their orientations as referred to the body of the patient are shown in figure 6, where it will be noticed that the zero reference line (from which all angular measurements are taken in a clockwise direction) oc-

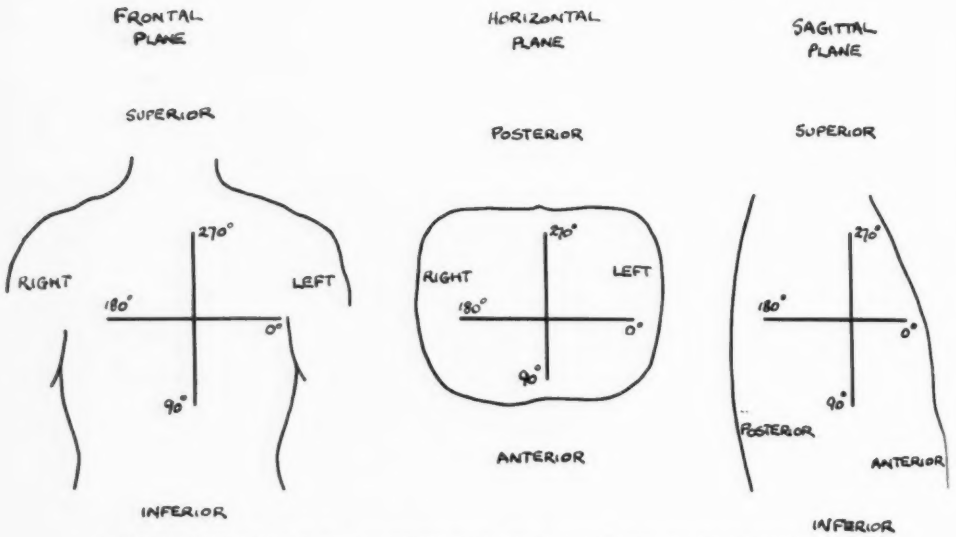


FIG. 6. Orientation of axes on planar projections according to the Helm notation.

cupies the same position in all planes, this position being the one originally proposed by Einthoven for the frontal plane projection. According to this notation the sagittal plane loops are presented as though viewing the heart through the right side of the thorax instead of from the left as recommended by the Committee on Electrocardiography of the American Heart Association.[18]

The path of the instantaneous cardiac electromotive force ($\hat{E}$) in space during the ventricular depolarization phase of the cardiac cycle is designated as the QRS s$\hat{E}$ loop by Bayley[19] and its projection on the frontal plane of the body as the QRS $\hat{E}$ loop (frontal). The spatial loops for the atrial and ventricular repolarization phases are similarly designated P s$\hat{E}$ and T s$\hat{E}$ respectively.

The symbols used to represent the vectorial quantities derived by computing areas under the curves of scalar tracings are those suggested by Bayley in an appendix to a paper by Ashman and Byer,[20] except that we have prefixed the initial letter of each plane of reference (F, H, or S). This necessitates one additional modification of Bayley's nomenclature, since he used the prefix 'S' to indicate spatial quantities for which we suggest the prefix letters (SP). Examples of this notation are:

$F\hat{A}_{QRS}$ ..... mean manifest axis angle of QRS as projected on the frontal plane and calculated from scalar tracing areas.

$FA_{QRS}$ ..... magnitude in microvolt-seconds of the above axis.

$F\hat{A}_{QRS-T}$ ..... manifest angle as projected on the frontal plane between the mean QRS axis and the mean T axis.

$F\hat{A}_{G}$ ..... mean manifest axis angle of the ventricular gradient as projected on the frontal plane.

$H\hat{A}_{P}$ ..... mean manifest axis angle of P on the horizontal plane.

$SA_{G}$ ..... magnitude in microvolt-seconds of mean axis of G on the sagittal plane.

$(SP)\hat{A}_{QRS-T}$ .. angle between the mean spatial axis of QRS and the mean spatial axis of T.

Of the 47 individuals examined by the lead field method 39 gave results that showed remarkable similarities and that constituted a closely knit group of data, whereas the re-

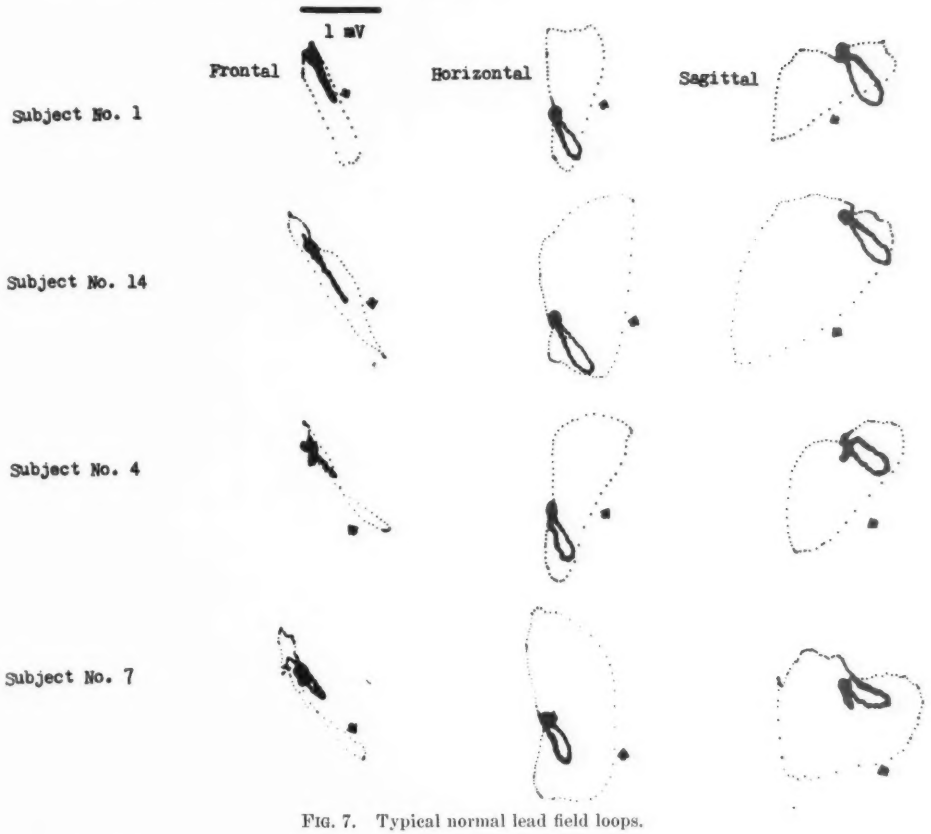


FIG. 7. Typical normal lead field loops.

maining 8 subjects gave loops and vectorial analytical values that obviously differed in varying degrees from the majority. For these reasons we have considered it prudent to analyze together the group of 39 cases in order to obtain the best estimates of standard mean values and to compare separately the remaining 8 with those values. This is in no way to suggest that the latter group consists of individuals having pathologic cardiac conditions, since clinically there was no evidence to warrant that assumption, but rather at present to regard them as possessing wider variations within the normal range and by examining each separately to attempt to assess the nature of the variation in each case.

*Qualitative Description of Loops*

Typical examples of lead field loops for the main group of 39 subjects are shown in figure 7. In the frontal plane the QRS loop is usually narrow and smooth in outline without marked indentations or other irregularities though occasionally these do occur as shown in the lowest of the 4 sets of tracings. The loop is characteristically inscribed in a clockwise direction with slower initial and terminal portions, either or both of which may rise slightly above the isoelectric point, but sometimes the loop may be of figure-of-eight shape or even inscribed wholly anticlockwise for reasons discussed below. The main axis of the loop, as measured from the isoelectric point to the tip, usually makes an angle of approximately 60° with the horizontal. The frontal plane T loop is commonly extremely narrow, lying in the same plane as QRS $\hat{E}$ and often enclosed within it. T $\hat{E}$ is

inscribed in the same direction as QRS Ê but lies entirely below the isoelectric point.

The P loop can sometimes be distinguished as a separate entity but no attempt has been made in this study to characterize it in detail.

In the horizontal plane QRS Ê is more widely open and remarkably smooth in contour. The initial forces are such that the loop is slowly inscribed and directed anteriorly, then sweeping anticlockwise to the patient's left and posteriorly, the course of the loop becomes almost directly anterior again in the returning limb. The T loop is smooth and widely open, often enclosed within QRS Ê and inscribed anticlockwise to the left. The main axes of the loops are, therefore, separated by a wide angle in the horizontal plane, the majority of QRS Ê posterior and all of TÊ being anterior to the isoelectric point.

In the sagittal plane projection QRS Ê passes initially anteriorly and sometimes slightly upward before sweeping infero-posteriorly to return almost directly anteriorly to the isoelectric position. The T loop is again wide open and inscribed clockwise entirely anteriorly to the isoelectric point. There is thus in this plane also a wide angle between the main axes of the 2 loops.

Quite frequently, as shown in the lowest of the 4 tracings in figure 7, the QRS and T loops in the sagittal plane (and more rarely in the horizontal) are incomplete and reveal that the commencements of the 2 loops arise at different points in space, the phenomenon that would be recorded on a scalar tracing as a segment deviation (cf. S-T deviation in lead B *supra*).

With relatively minor variations, therefore, the loops in space can be described as follows. QRS sÊ occupies a single plane lying chiefly anteroposteriorly almost perpendicular to the frontal plane of the body and making an angle of approximately 60° with the horizontal. The outline of the loop is usually smooth with the initial forces slowly inscribed in an almost exactly anterior direction and then, with increasing velocity, the resultant instantaneous electric activity sweeps inferiorly and to the patient's left before assuming a postero-inferior direction. The returni g limb of the spatial loop is upward and to t right with a slower terminal portion direct almost anteriorly.

The T loop in space also lies in a sing plane that is nearly identical with that QRS sÊ but the long axis is directed anterio ly instead of posteriorly. T sÊ is inscrib at a fairly constant speed with the initi forces passing infero-anteriorly and to t left before turning posteriorly and finally u ward, posteriorly and to the right.

*Main Axes of the Planar Loops*

Visual inspection of each QRS loop gene ally revealed an obvious elongation in one o other direction relative to the isoelectri point and hence an orientation about a mai loop axis. However, in some cases, especiall in hearts giving loops excessively rotated o their anteroposterior axes (as will be de scribed later), no such main loop axis could be defined by inspection and because of this difficulty recourse was had to a more objective method of assessment.

It was observed that where a well-marked "apex" was present in a horizontal or sagittal plane loop (whose long axis was, therefore, readily defined) it occurred at, or very close to, the mid-point in time of inscription of QRS Ê in that plane, i.e., the loop was roughly symmetrical in time and changed direction abruptly at or about the middle timing blip. We have consequently used this point for estimation of the main loop axis. By counting the timing blips on the horizontal and sagittal plane loops of a given individual, it is possible to decide which point in each plane most nearly corresponds to the mid-time blip of the loop in space and by joining this blip to the loop isoelectric point the directions of the main loop axes in the 2 planes are determined.

In the frontal plane the main axis often c incides with the line joining the isoelectr point to the most distal point on the loop, b not always so. Because of the almost "edg on" view of the spatial loop as projected o to this plane, the blips are too closely plac

for accurate counting but, by comparison with the corresponding horizontal and sagittal views, it is possible to decide which frontal plane blip represents most closely the actual spatial mid-time interval and this one was used for measuring the main loop axis in this plane.

The same method could obviously not be applied to the more slowly inscribed T loops but these were of such regular elliptical shapes that it was considered justifiable to take the direction of the axis as that of a line joining the isoelectric point to the loop tip in each case.

The values obtained for these axis angles and for the angle between QRS and T for each individual in all 3 planes are given in table 2 and, since the frequency distributions of the values approximate to the normal (Gaussian) type, it is permissible to quote in addition the corresponding standard deviations of the means and the 95 per cent probability limits.

The mean main axis for QRS sÊ is seen to lie downward, backward and to the left so as to give projections on the frontal plane of 62° (S.D. 12), on the horizontal plane of 301° (S.D. 16) and on the sagittal plane of 127° (S.D. 14). Consequently, 95 per cent of all individuals of the population sampled are likely to have frontal plane axes lying between 38° and 86°, horizontal plane axes lying between 269° and 333° and sagittal plane axes between 99° and 155.°

The mean main axis of T sÊ lies downward, forward and to the left such that the frontal plane projection is 60° (S.D. 9), the horizontal projection 62° (S.D. 15) and the sagittal 42° (S.D. 18), so that 95 per cent of these subjects are likely to have frontal plane T axes lying between 42° and 78°, horizontal axes between 32° and 92° and sagittal between 7° and 79.°

Because of these normal relative spatial positions of the QRS and T loops we have throughout adopted the convention that when describing the spatial or planar angle separating QRS from T the angle shall be regarded as positive when QRS lies posterior or inferior to T.

The mean angle between the main QRS and T loop axes in the frontal plane is very small (+2°, S.D. 12), since the 2 loops lie almost perpendicular to this plane, and values lying outside the limits of −22° and +26° are likely to occur only once in every 20 individuals of this group.

In the horizontal plane, where the QRS loop is oriented chiefly posteriorly and the T loop entirely anteriorly, the mean angle between the main loop axes is +121° (S.D. 24) and, similarly, in the sagittal plane the angle is + 85° (S.D. 21) so that only 5 per cent of values are likely to lie outside the limits of +73° and +169° in the horizontal plane and +43° and +127° in the sagittal.

From the QRS-T angles as projected on any 2 planes the true angle in space between the main axes of QRS sÊ and T sÊ can be calculated by the method of Helm and Fowler,[21] and these spatial angles are also given in table 2. The angles quoted are the means obtained for each subject by utilizing in pairs the projected values on all 3 planes. As would be expected from the orientation of the loops, the spatial angle of +83° (S.D. 21) is slightly smaller than the sagittal plane angle, the mean individual difference being −2° (S.D. 9).

### *Calculation of Electric Axis Vectors from Lead Field Scalar Tracings*

Before each planar lead field loop was displayed on the cardioscope screen the corresponding X- and Y-axis rectangular components were recorded directly as fast speed scalar tracings. From these, by the usual method of algebraic summation of areas enclosed by the curves, the net electric activity, in microvolt-seconds, associated with each phase of the cardiac cycle was determined for each of the rectangular axis components and, from these, the mean manifest vectorial electric axis in each plane. The angular directions of these vectors as projected on the 3 planes ($F\hat{A}_{QRS}$, $F\hat{A}_{T}$ etc.) are given in

TABLE 2.—*Cardiac Electric Axis Data for Main Group of Thirty-Nine Individuals*

| Subject No. | MAIN LOOP AXIS ANGLE | | | | | | | | | | MEAN MANIFEST ELECTRICAL AXIS ANGLE FROM SCALAR AREAS | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | QRS | | | T | | | QRS - T | | | Spatial QRS - T | $\hat{A}_P$ | | | $\hat{A}_{QRS}$ | | | $\hat{A}_T$ | | | $\hat{A}_U$ | | | $\hat{A}_{QRS-T}$ | | | Spatial QRS - T |
| | F | H | S | F | H | S | F | H | S | | F | H | S | F | H | S | F | H | S | F | H | S | F | H | S | |
| 1. | 71 | 295 | 122 | 64 | 62 | 55 | + 7 | +127 | + 67 | + 67 | 77 | 0 | 90 | 62 | 290 | 146 | 56 | 60 | 40 | 57 | 28 | 71 | + 6 | +130 | +106 | + 97 |
| 2. | 62 | 292 | 129 | 56 | 71 | 3 | + 6 | 139 | 126 | 116 | 88 | 0 | 90 | 84 | 280 | 122 | 59 | 82 | 14 | 77 | 66 | 63 | +25 | 162 | 108 | 102 |
| 3. | 69 | 288 | 128 | 65 | 53 | 50 | + 4 | 125 | 78 | 74 | 0 | 69 | 0 | 63 | 293 | 140 | 70 | 73 | 41 | 68 | 55 | 61 | - 7 | 140 | 99 | 95 |
| 4. | 49 | 327 | 110 | 52 | 65 | 28 | - 3 | 98 | 82 | 74 | 79 | 49 | 86 | 49 | 334 | 114 | 47 | 72 | 19 | 48 | 46 | 47 | + 2 | 98 | 95 | 81 |
| 5. | 54 | 313 | 125 | 56 | 68 | 43 | - 2 | 115 | 82 | 78 | 82 | 68 | 71 | 42 | 307 | 146 | 61 | 74 | 28 | 53 | 39 | 58 | -19 | 127 | 118 | 105 |
| 6. | 61 | 299 | 123 | 66 | 81 | 29 | - 5 | 142 | 94 | 98 | 86 | 63 | 83 | 66 | 306 | 122 | 78 | 84 | 28 | 72 | 66 | 54 | -12 | 138 | 94 | 87 |
| 7. | 57 | 314 | 120 | 48 | 63 | 20 | + 9 | 109 | 100 | 87 | 80 | 63 | 73 | 45 | 282 | 168 | 45 | 72 | 18 | 45 | 65 | 26 | 0 | 150 | 150 | 139 |
| 8. | 58 | 288 | 127 | 53 | 48 | 60 | + 5 | 120 | 67 | 73 | 86 | 59 | 84 | 85 | 273 | 146 | 48 | 47 | 46 | 55 | 29 | 69 | +37 | 134 | 100 | 91 |
| 9. | 48 | 310 | 125 | 66 | 75 | 37 | -18 | 125 | 88 | 88 | 85 | 34 | 86 | 58 | 305 | 133 | 61 | 74 | 27 | 60 | 44 | 60 | - 3 | 129 | 106 | 101 |
| 10. | 54 | 320 | 112 | 64 | 64 | 34 | -10 | 104 | 74 | 69 | 45 | 45 | 45 | 50 | 310 | 136 | 50 | 70 | 24 | 50 | 51 | 45 | 0 | 120 | 112 | 97 |
| 11. | 70 | 291 | 126 | 51 | 70 | 25 | +19 | 139 | 101 | 99 | 81 | 27 | 85 | 60 | 292 | 145 | 48 | 77 | 14 | 53 | 60 | 37 | +12 | 145 | 131 | 121 |
| 12. | 49 | 340 | 84 | 69 | 35 | 67 | -20 | 55 | 17 | 31 | 27 | 56 | 19 | 58 | 317 | 121 | 63 | 66 | 41 | 61 | 37 | 68 | - 5 | 109 | 80 | 71 |
| 13. | 56 | 334 | 110 | 55 | 46 | 52 | + 1 | 72 | 58 | 48 | 87 | 72 | 81 | 52 | 326 | 118 | 54 | 57 | 42 | 53 | 39 | 59 | - 2 | 91 | 76 | 66 |
| 14. | 57 | 303 | 125 | 58 | 56 | 45 | - 1 | 113 | 80 | 73 | 50 | 39 | 56 | 45 | 323 | 127 | 51 | 63 | 32 | 50 | 50 | 45 | - 6 | 100 | 95 | 80 |
| 15. | 67 | 297 | 127 | 45 | 73 | 6 | +22 | 136 | 121 | 119 | 56 | 50 | 52 | 70 | 290 | 135 | 11 | 72 | 4 | 49 | 42 | 52 | +59 | 142 | 131 | 119 |
| 16. | 48 | 314 | 110 | 50 | 66 | 29 | - 2 | 112 | 81 | 78 | 67 | 53 | 61 | 42 | 302 | 152 | 42 | 74 | 15 | 42 | 62 | 26 | 0 | 132 | 137 | 119 |
| 17. | 76 | 310 | 164 | 62 | 33 | 68 | +14 | 83 | 96 | 66 | 66 | 65 | 47 | 37 | 309 | 148 | 53 | 65 | 31 | 48 | 37 | 56 | - 16 | 116 | 117 | 92 |
| 18. | 81 | 302 | 110 | 59 | 56 | 50 | +22 | 114 | 60 | 58 | 82 | 14 | 88 | 81 | 280 | 133 | 62 | 72 | 31 | 69 | 61 | 55 | + 19 | 152 | 102 | 101 |
| 19. | 73 | 276 | 140 | 55 | 36 | 33 | +18 | 120 | 107 | 97 | 45 | 53 | 37 | 47 | 298 | 151 | 29 | 59 | 19 | 36 | 23 | 60 | +18 | 121 | 132 | 106 |
| 20. | 25 | 306 | 142 | 58 | 20 | 79 | -33 | 74 | 63 | 59 | 66 | 45 | 65 | 24 | 307 | 162 | 46 | 31 | 60 | 44 | 20 | 70 | - 22 | 84 | 102 | 76 |
| 21. | 70 | 277 | 134 | 67 | 70 | 26 | + 3 | 153 | 108 | 115 | 90 | 90 | 70 | 89 | 271 | 126 | 61 | 82 | 17 | 77 | 78 | 43 | + 28 | 171 | 109 | 110 |
| 22. | 75 | 297 | 125 | 69 | 76 | 23 | + 6 | 139 | 102 | 90 | 73 | 34 | 78 | 70 | 296 | 128 | 40 | 75 | 13 | 53 | 64 | 33 | +30 | 139 | 115 | 109 |
| 23. | 82 | 280 | 132 | 80 | 85 | 45 | + 2 | 165 | 87 | 96 | 63 | 0 | 63 | 83 | 276 | 140 | 86 | 87 | 33 | 85 | 79 | 67 | - 3 | 171 | 107 | 107 |
| 24. | 65 | 286 | 140 | 77 | 65 | 58 | -12 | 139 | 82 | 82 | 75 | 54 | 68 | 59 | 289 | 150 | 71 | 73 | 42 | 69 | 61 | 54 | -12 | 144 | 108 | 108 |
| 25. | 55 | 306 | 140 | 54 | 75 | 52 | + 1 | 129 | 88 | 92 | 72 | 53 | 80 | 40 | 307 | 148 | 55 | 65 | 33 | 50 | 37 | 58 | -15 | 118 | 115 | 99 |
| 26. | 87 | 270 | 156 | 61 | 75 | 40 | +26 | 165 | 116 | 133 | 74 | 56 | 77 | 70 | 292 | 132 | 53 | 74 | 21 | 60 | 59 | 46 | +17 | 142 | 111 | 108 |
| 27. | 50 | 306 | 132 | 61 | 79 | 38 | -11 | 133 | 94 | 97 | 73 | 31 | 79 | 39 | 291 | 162 | 71 | 78 | 31 | 60 | 36 | 67 | -32 | 147 | 131 | 125 |
| 28. | 69 | 307 | 131 | 68 | 69 | 70 | + 1 | 122 | 61 | 63 | 83 | 63 | 76 | 68 | 320 | 108 | 64 | 77 | 26 | 66 | 68 | 42 | + 4 | 117 | 82 | 78 |
| 29. | 71 | 298 | 126 | 70 | 60 | 66 | + 1 | 122 | 60 | 59 | 72 | 0 | 90 | 66 | 301 | 126 | 62 | 60 | 47 | 63 | 38 | 68 | + 4 | 119 | 79 | 75 |
| 30. | 64 | 294 | 141 | 60 | 60 | 74 | + 4 | 126 | 67 | 72 | 85 | 72 | 75 | 62 | 286 | 151 | 65 | 67 | 43 | 64 | 39 | 69 | - 3 | 141 | 108 | 98 |
| 31. | 47 | 307 | 148 | 51 | 59 | 44 | - 4 | 112 | 104 | 91 | 40 | 50 | 38 | 42 | 294 | 159 | 44 | 67 | 23 | 43 | 50 | 38 | - 2 | 133 | 136 | 115 |
| 32. | 58 | 288 | 136 | 47 | 77 | 27 | +11 | 149 | 109 | 98 | 79 | 68 | 65 | 71 | 278 | 158 | 57 | 75 | 24 | 61 | 60 | 45 | +14 | 157 | 134 | 129 |
| 33. | 54 | 317 | 114 | 47 | 52 | 24 | + 7 | 95 | 90 | 75 | 55 | 30 | 68 | 58 | 338 | 105 | 30 | 63 | 17 | 47 | 38 | 53 | +28 | 85 | 88 | 77 |
| 34. | 65 | 288 | 130 | 73 | 60 | 65 | - 8 | 132 | 65 | 68 | 80 | 76 | 51 | 68 | 277 | 165 | 69 | 64 | 52 | 68 | 51 | 64 | - 1 | 147 | 113 | 112 |
| 35. | 70 | 296 | 133 | 68 | 79 | 29 | + 2 | 143 | 104 | 101 | 86 | 67 | 77 | 65 | 295 | 135 | 62 | 79 | 21 | 63 | 72 | 32 | + 3 | 144 | 114 | 111 |
| 36. | 80 | 271 | 129 | 61 | 71 | 30 | +19 | 160 | 99 | 120 | 111 | 157 | 81 | 95 | 265 | 138 | 48 | 77 | 16 | 72 | 70 | 50 | +47 | 172 | 122 | 120 |
| 37. | 64 | 301 | 114 | 53 | 66 | 26 | +11 | 125 | 88 | 86 | 72 | 22 | 83 | 48 | 321 | 126 | 59 | 76 | 22 | 51 | 18 | 75 | -11 | 115 | 104 | 93 |
| 38. | 62 | 331 | 112 | 81 | 77 | 42 | -19 | 106 | 70 | 60 | 68 | 27 | 79 | 60 | 349 | 97 | 65 | 82 | 19 | 63 | 75 | 29 | - 5 | 93 | 78 | 73 |
| 39. | 50 | 299 | 132 | 56 | 40 | 56 | - 6 | 101 | 76 | 69 | 84 | 19 | 87 | 54 | 298 | 145 | 47 | 60 | 32 | 48 | 43 | 50 | + 7 | 122 | 113 | 98 |
| **Mean** | 62° | 301° | 127° | 60° | 62° | 43° | + 2° | +121° | + 85° | + 83° | 71° | 49° | 69° | 60° | 299° | 138° | 55° | 70° | 28° | 58° | 50° | 53° | + 5° | +131° | +109° | +100° |
| | 12° | 16° | 14° | 9° | 15° | 18° | 12° | 24° | 21° | 21° | 20° | 29° | 20° | 16° | 19° | 17° | 14° | 16° | 12° | 11° | 16° | 11° | 10° | 21° | 14° | 17° |

TABLE 3.—*Magnitudes (in microvolt-seconds) of Mean Manifest and Spatial Electric Cardiac Vectors Calculated from Scalar Tracing Areas*

| Subject No. | $A_{QRS}$ | | | $A_T$ | | | $A_G$ | | | $(SP)A_{QRS}$ | $(SP)A_T$ | $(SP)A_G$ | $(SP)A_{'total'\ QRS}$ | $\frac{(SP)A_T}{(SP)A_{'total'\ QRS}}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F | H | S | F | H | S | F | H | S | | | | | |
| 1. | 27 | 39 | 43 | 63 | 72 | 82 | 90 | 55 | 80 | 46 | 89 | 93 | 58 | 1.5 |
| 2. | 64 | 41 | 76 | 24 | 84 | 86 | 86 | 47 | 94 | 76 | 86 | 96 | 93 | 0.9 |
| 3. | 18 | 21 | 25 | 50 | 57 | 72 | 68 | 43 | 72 | 26 | 74 | 76 | 56 | 1.3 |
| 4. | 33 | 25 | 27 | 25 | 54 | 54 | 58 | 56 | 59 | 35 | 57 | 71 | 45 | 1.3 |
| 5. | 36 | 45 | 43 | 46 | 78 | 85 | 80 | 62 | 75 | 51 | 88 | 89 | 59 | 1.5 |
| 6. | 30 | 21 | 32 | 32 | 60 | 67 | 61 | 46 | 72 | 35 | 68 | 74 | 50 | 1.4 |
| 7. | 4 | 14 | 14 | 28 | 65 | 65 | 32 | 53 | 53 | 14 | 68 | 58 | 54 | 1.3 |
| 8. | 12 | 18 | 22 | 55 | 54 | 57 | 65 | 43 | 57 | 22 | 68 | 68 | 44 | 1.5 |
| 9. | 32 | 30 | 37 | 33 | 60 | 65 | 65 | 46 | 64 | 40 | 67 | 73 | 50 | 1.3 |
| 10. | 28 | 28 | 31 | 47 | 86 | 88 | 75 | 75 | 81 | 35 | 93 | 94 | 43 | 2.2 |
| 11. | 13 | 17 | 19 | 16 | 48 | 49 | 29 | 36 | 39 | 20 | 47 | 43 | 45 | 1.0 |
| 12. | 30 | 22 | 29 | 39 | 44 | 53 | 69 | 42 | 65 | 34 | 56 | 74 | 47 | 1.2 |
| 13. | 31 | 23 | 27 | 65 | 71 | 80 | 96 | 74 | 90 | 34 | 88 | 106 | 55 | 1.6 |
| 14. | 23 | 20 | 20 | 63 | 88 | 92 | 86 | 86 | 93 | 26 | 100 | 108 | 45 | 2.2 |
| 15. | 35 | 35 | 46 | 21 | 64 | 62 | 49 | 43 | 47 | 48 | 64 | 57 | 61 | 1.1 |
| 16. | 23 | 33 | 32 | 51 | 136 | 134 | 74 | 115 | 113 | 36 | 140 | 125 | 52 | 2.7 |
| 17. | 26 | 34 | 31 | 49 | 70 | 75 | 75 | 64 | 67 | 37 | 80 | 85 | 79 | 1.0 |
| 18. | 16 | 15 | 22 | 31 | 48 | 53 | 46 | 35 | 53 | 22 | 55 | 55 | 48 | 1.1 |
| 19. | 13 | 19 | 20 | 19 | 33 | 29 | 32 | 28 | 22 | 21 | 34 | 34 | 41 | 0.8 |
| 20. | 12 | 19 | 16 | 110 | 90 | 92 | 122 | 94 | 89 | 20 | 120 | 127 | 32 | 3.7 |
| 21. | 41 | 30 | 50 | 33 | 105 | 108 | 71 | 75 | 101 | 51 | 110 | 102 | 67 | 1.6 |
| 22. | 32 | 26 | 38 | 38 | 110 | 108 | 67 | 91 | 99 | 40 | 110 | 105 | 78 | 1.4 |
| 23. | 16 | 19 | 25 | 23 | 56 | 43 | 39 | 17 | 42 | 25 | 43 | 42 | 36 | 1.2 |
| 24. | 6 | 9 | 10 | 33 | 35 | 46 | 38 | 28 | 44 | 10 | 47 | 45 | 30 | 1.6 |
| 25. | 22 | 29 | 27 | 43 | 60 | 64 | 64 | 52 | 58 | 32 | 70 | 71 | 38 | 1.8 |
| 26. | 26 | 24 | 33 | 35 | 75 | 78 | 60 | 58 | 72 | 34 | 80 | 78 | 39 | 2.1 |
| 27. | 13 | 28 | 27 | 25 | 40 | 45 | 36 | 22 | 34 | 29 | 46 | 38 | 37 | 1.2 |
| 28. | 32 | 16 | 32 | 52 | 98 | 107 | 84 | 92 | 116 | 34 | 109 | 120 | 61 | 1.8 |
| 29. | 37 | 29 | 42 | 80 | 76 | 96 | 116 | 67 | 110 | 45 | 104 | 123 | 68 | 1.5 |
| 30. | 19 | 32 | 35 | 58 | 62 | 78 | 78 | 43 | 74 | 36 | 81 | 82 | 73 | 1.1 |
| 31. | 13 | 26 | 25 | 42 | 78 | 78 | 56 | 64 | 62 | 27 | 83 | 75 | 52 | 1.6 |
| 32. | 18 | 43 | 46 | 52 | 108 | 112 | 70 | 70 | 86 | 46 | 116 | 93 | 66 | 1.8 |
| 33. | 67 | 39 | 58 | 42 | 83 | 77 | 107 | 94 | 97 | 69 | 86 | 122 | 87 | 1.0 |
| 34. | 5 | 18 | 19 | 74 | 59 | 88 | 79 | 45 | 82 | 19 | 91 | 86 | 30 | 3.0 |
| 35. | 14 | 14 | 18 | 36 | 86 | 92 | 50 | 77 | 87 | 19 | 92 | 89 | 45 | 2.0 |
| 36. | 32 | 36 | 48 | 28 | 82 | 83 | 55 | 46 | 69 | 48 | 85 | 70 | 59 | 1.4 |
| 37. | 39 | 33 | 36 | 15 | 33 | 35 | 54 | 35 | 43 | 45 | 35 | 55 | 51 | 0.7 |
| 38. | 20 | 10 | 17 | 33 | 91 | 93 | 53 | 90 | 100 | 20 | 96 | 102 | 36 | 2.7 |
| 39. | 15 | 19 | 21 | 49 | 67 | 68 | 64 | 58 | 62 | 22 | 76 | 75 | 46 | 1.7 |
| Mean | 25 | 26 | 31 | 43 | 70 | 75 | 67 | 58 | 72 | 34 | 80 | 82 | 53 | 1.6 |
| S.D. | 13 | 9 | 13 | 19 | 23 | 23 | 22 | 22 | 23 | 14 | 24 | 25 | 15 | 0.6 |

table 2 and the corresponding magnitudes ($FA_{QRS}$, $FA_T$ etc.) in table 3, while mean directions and magnitudes of these manifest vectors are shown diagrammatically in figure 8.

The average mean manifest electric axis angle for QRS in the frontal plane as calculated from the scalar tracings (60°, S.D. 16) does not differ significantly from that obtained by direct measurement of the main loop axis nor is there any significant difference between the individual pairs of observations, but the loop axis angle for T in each case is significantly greater than the corresponding value from scalar areas by an average of 6° ($t = 3.8$, $p < 0.01$).

Similarly, in the horizontal and sagittal planes there is no difference between the QRS

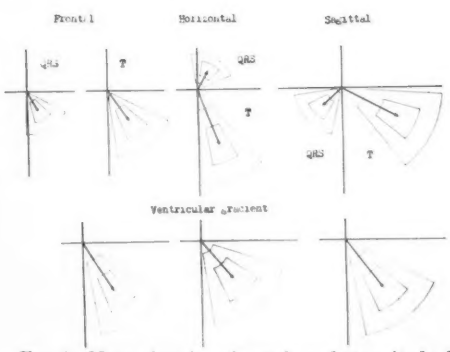


FIG. 8. Mean electric axis angle and magnitude for QRS, T, and ventricular gradient calculated from lead field scalar tracings for the main group of subjects showing the limits within which 65 per cent and 95 per cent of the individual values may be expected to lie.

TABLE 4.—*Comparison of Mean Vectorial Electric Axis Angles and Magnitudes from Scalar Tracing Areas by Different Electrode Placements*

**FRONTAL PLANE**

| | $\hat{FA}_P$ | $\hat{FA}_{QRS}$ | $FA_{QRS}$ | $\hat{FA}_T$ | $FA_T$ | $\hat{FA}_G$ | $FA_G$ | $\hat{FA}_{QRS-T}$ |
|---|---|---|---|---|---|---|---|---|
| Lead Field | 71° | 60° | 25 mvs | 55° | 43 mvs | 58° | 67 mvs | +5° |
| Grishman | 66 | 45 | 16 | 40 | 22 | 43 | 38 | +5 |
| Leads I - II | 60 | 68 | 18 | 40 | 26 | 53 | 41 | +28 |
| Leads I - III | 58 | 69 | 18 | 41 | 24 | 54 | 40 | +28 |

**HORIZONTAL PLANE**

| | $\hat{HA}_P$ | $\hat{HA}_{QRS}$ | $HA_{QRS}$ | $\hat{HA}_T$ | $HA_T$ | $\hat{HA}_G$ | $HA_G$ | $\hat{HA}_{QRS-T}$ |
|---|---|---|---|---|---|---|---|---|
| Lead Field | 49° | 299° | 26 mvs | 70° | 70 mvs | 50° | 58 mvs | +131° |
| Grishman | 25 | 4 | 11 | 13 | 17 | 10 | 28 | +9 |

**SAGITTAL PLANE**

| | $\hat{SA}_P$ | $\hat{SA}_{QRS}$ | $SA_{QRS}$ | $\hat{SA}_T$ | $SA_T$ | $\hat{SA}_G$ | $SA_G$ | $\hat{SA}_{QRS-T}$ |
|---|---|---|---|---|---|---|---|---|
| Lead Field | 69° | 138° | 31 mvs | 28° | 75 mvs | 53° | 72 mvs | +110 |
| Grishman | 78 | 86 | 12 | 75 | 15 | 80 | 26 | +11 |

main loop axis angles and the calculated mean vectorial angles, but for the T loops the scalar area vectors place the axes more anteriorly by approximately 8° in the horizontal and 15° in the sagittal plane. In consequence, the spatial QRS-T angle as measured directly from the main loop axes is, on the average, 17° smaller than that obtained by area computation. There is, however, a marked positive correlation between the 2 methods of assessment ($r = 0.48$, $t = 3.4$, $p < 0.01$).

The ventricular gradient for each individual has been calculated by the standard method of algebraic summation of the QRS and T areas on the scalar tracings of each plane and the direction and magnitude of the resultant vector determined. These values are included in tables 2 and 3 from which it is seen that the gradient is directed downward, forward and to the left in every case with mean projected angles of 58° (S.D. 11) in the frontal plane, 50° (S.D. 16) in the horizontal plane and 53° (S.D. 13) in the sagittal.

The manifest electric vector magnitudes in each plane are greater for $A_T$ than for $A_{QRS}$ (see table 3) but this is a natural consequence of the difference in shape and direction of the QRS and T loops in relation to the isoelectric point. Because of these differences the T component of a scalar tracing in any of the 3 rectangular planes of space is almost invariably monophasic and, by convention, written upright. Hence the total electric activity represented by the scalar T wave is regarded as positive and equal to the total area under the curve. In the case of the QRS loop, on the other hand, the electric activity associated with the initial and terminal events is often oriented such that it becomes written as the negative Q and S deflections, so that the net electric activity, as calculated from the algebraic summation of areas under the QRS complex, is considerably less than the total.

In order to attempt to measure the magnitude of the total electric activity associated with the depolarization process as

TABLE 5.—*Cardiac Electric Axis Data for Subsidiary Group of Eight Individuals*

ANGLES

| Subject No. | MAIN LOOP AXIS ANGLE: QRS F | QRS H | QRS S | T F | T H | T S | QRS - T F | QRS - T H | QRS - T S | Spatial QRS - T | MEAN MANIFEST ELECTRICAL AXIS ANGLE FROM SCALAR AREAS: $\hat{A}_P$ F | $\hat{A}_P$ H | $\hat{A}_P$ S | $\hat{A}_{QRS}$ F | $\hat{A}_{QRS}$ H | $\hat{A}_{QRS}$ S | $\hat{A}_T$ F | $\hat{A}_T$ H | $\hat{A}_T$ S | $\hat{A}_G$ F | $\hat{A}_G$ H | $\hat{A}_G$ S | $\hat{A}_{QRS-T}$ F | $\hat{A}_{QRS-T}$ H | $\hat{A}_{QRS-T}$ S | Spatial QRS - T |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. | 30 | 290 | 164 | 61 | 70 | 43 | - 31 | +140 | +121 | +114 | 74 | 12 | 87 | 334 | 283 | 186 | 55 | 71 | 27 | 46 | 49 | 42 | - 81 | +148 | +159 | +143 |
| B. | 73 | 350 | 93 | 57 | 71 | 30 | +16 | 81 | 63 | 63 | 83 | 76 | 64 | 70 | 55 | 62 | 52 | 74 | 21 | 62 | 69 | 36 | + 18 | + 19 | + 41 | + 41 |
| C. | 63 | 301 | 137 | 88 | 74 | 43 | - 25 | 133 | 94 | 74 | 78 | 45 | 78 | 55 | 300 | 141 | 69 | 80 | 26 | 59 | 337 | 104 | - 14 | +140 | +115 | +108 |
| D. | 100 | --- | 107 | 53 | 42 | 53 | +107 | --- | >4 | 106 | 56 | 0 | 90 | 163 | 133 | 16 | 41 | 46 | 41 | 45 | 52 | 39 | +122 | - 87 | - 25 | - 84 |
| E. | 74 | 309 | 113 | 86 | 345 | 106 | - 12 | 36 | 7 | 16 | 83 | 45 | 82 | 88 | 278 | 100 | 59 | 41 | 63 | 71 | 32 | 78 | + 29 | +123 | + 37 | + 42 |
| F. | 64 | 348 | 91 | 62 | 64 | 47 | + 2 | 76 | 44 | 47 | 78 | 68 | 67 | 71 | 24 | 81 | 57 | 68 | 33 | 62 | 62 | 45 | +14 | + 44 | + 48 | + 46 |
| G. | 317 | 338 | 255 | 46 | 58 | 22 | - 89 | 80 | 233 | 100 | 86 | 72 | 79 | 354 | 329 | 191 | 54 | 72 | 25 | 37 | 56 | 26 | - 60 | +103 | +166 | +100 |
| H. | 62 | 28 | 71 | 59 | 42 | 58 | + 3 | 14 | 13 | 8 | 90 | 90 | 64 | 67 | 350 | 94 | 70 | 58 | 59 | 69 | 36 | 74 | - 3 | + 68 | + 35 | + 34 |
| Mean of main group | 62 | 301 | 127 | 60 | 62 | 43 | + 2 | +121 | + 85 | + 83 | 71 | 49 | 69 | 60 | 299 | 138 | 55 | 70 | 28 | 58 | 50 | 53 | + 5 | +131 | +109 | +100 |

MAGNITUDES
(microvolt-seconds)

| Subject No. | $A_{QRS}$ F | $A_{QRS}$ H | $A_{QRS}$ S | $A_T$ F | $A_T$ H | $A_T$ S | $A_G$ F | $A_G$ H | $A_G$ S | $(SP)A_{QRS}$ | $(SP)A_T$ | $(SP)A_G$ | $(SP)A_{\text{'total' QRS}}$ | $\frac{(SP)A_T}{(SP)A_{\text{'total' QRS}}}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. | 10 | 44 | 42 | 55 | 92 | 98 | 57 | 60 | 61 | 44 | 103 | 73 | 55 | 1.9 |
| B. | 40 | 24 | 43 | 33 | 71 | 73 | 72 | 94 | 109 | 45 | 76 | 113 | 54 | 1.4 |
| C. | 54 | 62 | 70 | 19 | 39 | 42 | 72 | 41 | 64 | 76 | 43 | 74 | 76 | 0.6 |
| D. | 5 | 8 | 5 | 65 | 70 | 67 | 62 | 70 | 72 | 8 | 82 | 83 | 40 | 2.1 |
| E. | 20 | 4 | 21 | 29 | 20 | 28 | 48 | 18 | 46 | 20 | 32 | 49 | 52 | 0.6 |
| F. | 30 | 11 | 29 | 47 | 68 | 75 | 77 | 77 | 96 | 30 | 79 | 103 | 55 | 1.4 |
| G. | 9 | 10 | 6 | 21 | 40 | 41 | 27 | 39 | 36 | 10 | 43 | 42 | 32 | 1.3 |
| H. | 31 | 12 | 29 | 34 | 22 | 37 | 65 | 29 | 63 | 31 | 39 | 67 | 52 | 0.8 |
| Mean of main group | 25 | 26 | 31 | 43 | 70 | 75 | 67 | 58 | 72 | 34 | 80 | 82 | 53 | 1.6 |

compared with that of repolarization, an additional vectorial assessment has been ages recorded by the latter system are much smaller than those by the lead field technic. made for each subject by assuming the total area enclosed by the scalar QRS complex to be positive irrespective of its relationship to the isoelectric line. In this way a quantity more directly comparable in magnitude with the T vector is obtained. From the magnitudes of this so-called "total" QRS vector as projected on any 2 planes its spatial magnitude can be calculated and these values are also given in table 3 together with the ratios of (SP) $A_T$ to (SP) $A_{\text{"total" QRS}}$. It is seen that the values for this ratio are fairly closely grouped around a mean of 1.6 (S.D. 1.6).

An attempt has also been made to determine the manifest electric axis angle for P by area computation but the difficulty of measuring the small areas involved greatly limits the accuracy of such estimations. However, the tentative results are added to table 5 where the mean values are seen to be: for the frontal plane, 71° (S.D. 20), for the horizontal plane, 49° (S.D. 29) and for the sagittal plane, 69° (S.D. 20).

The vectorial electric axis angles and magnitudes in the frontal plane have also been calculated for this group of subjects from scalar tracings of leads I - II and I - III and for all 3 planes from tracings by the Grishman "cube" system of electrode placement. The mean values for these determinations are compared with the corresponding lead field figures in table 4.

The most noteworthy features of this comparison are that the lead field system gives a mean frontal plane axis angle for QRS intermediate between those of the Grishman system and the standard limb leads but a T axis angle greater than either of the other methods. In the horizontal plane a remarkable difference is seen in the mean values for the manifest QRS-T angle, which is +131° and +9° for the lead field and "cube" system leads respectively, with a corresponding difference in the sagittal plane. The anteroposterior component of the spatial electric

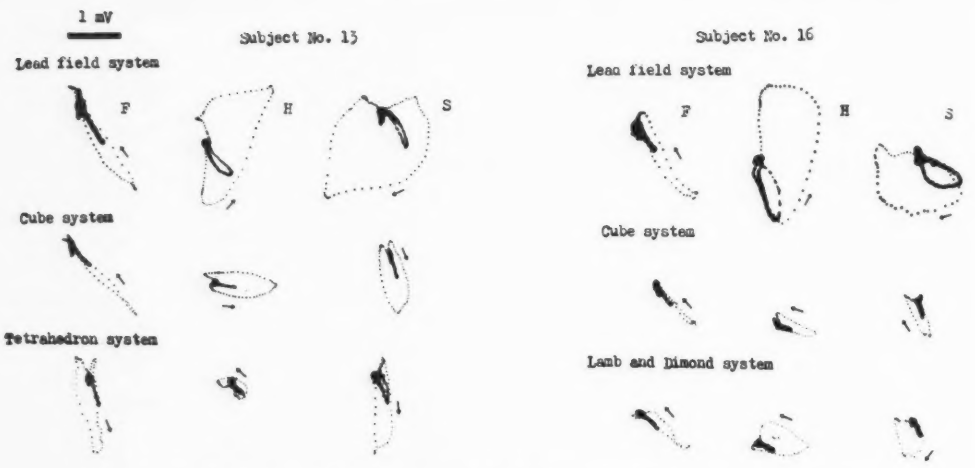


FIG. 9. Typical lead field loops compared with those obtained by the "cube," "tetrahedron," and Lamb and Dimond systems.

activity relative to the transverse and vertical components is grossly minimized by the Grishman method and in all planes the voltages recorded by the latter system are much smaller than those by the lead field technic.

Representative loops from the subsidiary group of 8 subjects are shown in figure 15 and their full analytic data in table 5. These findings will be discussed in detail at the end of the next section.

## DISCUSSION

### *Main Group of Subjects*

The lead field loops presented here differ fundamentally from those obtained using the "cube" system of electrode placement[22] or the "equilateral tetrahedron" system.[23] The anteroposterior component of the horizontal and sagittal planes is greatly increased in amplitude, so that the QRS loop in the horizontal plane becomes oriented chiefly anteroposteriorly instead of transversely as in the other systems, and the sagittal plane chiefly postero-inferiorly instead of vertically. These differences are illustrated in figure 9. The frontal plane loops given by all 3 technics are very similar except for the greater voltages recorded by the lead field electrodes. In the Grishman horizontal and sagittal planes minimal anteroposterior activity results in closed T "loops" and the manifest difference on any plane between the main loop axes of QRS and T is very small, both loops appearing to occupy the same plane in space.

In figure 9 the lead field loops are also compared with those resulting from the method of Lamb and Dimond[12] who used as a sagittal lead a single electrode placed anteriorly in the midline at the level of L2 and another on the back immediately posterior to it. Their sagittal and horizontal plane loops have greater anteroposterior amplitudes than those given by the "cube" and "tetrahedron" systems, but not nearly so great as those of the lead field loops.

While the present work was in progress, other authors have published preliminary results using multiple dorsal and ventral chest electrodes as recommended by McFee and Johnston.[4] Abildskov and Pence[24] compared spatial loops obtained using the tetrahedron reference frame with those resulting from the employment of banks of anterior and posterior chest electrodes. Their sagittal plane loops derived with these so-called "corrected" leads were comparable in shape with the lead field loops presented here. Reynolds and co-workers,[15] by means of 63-electrode grids, also obtained similar results.

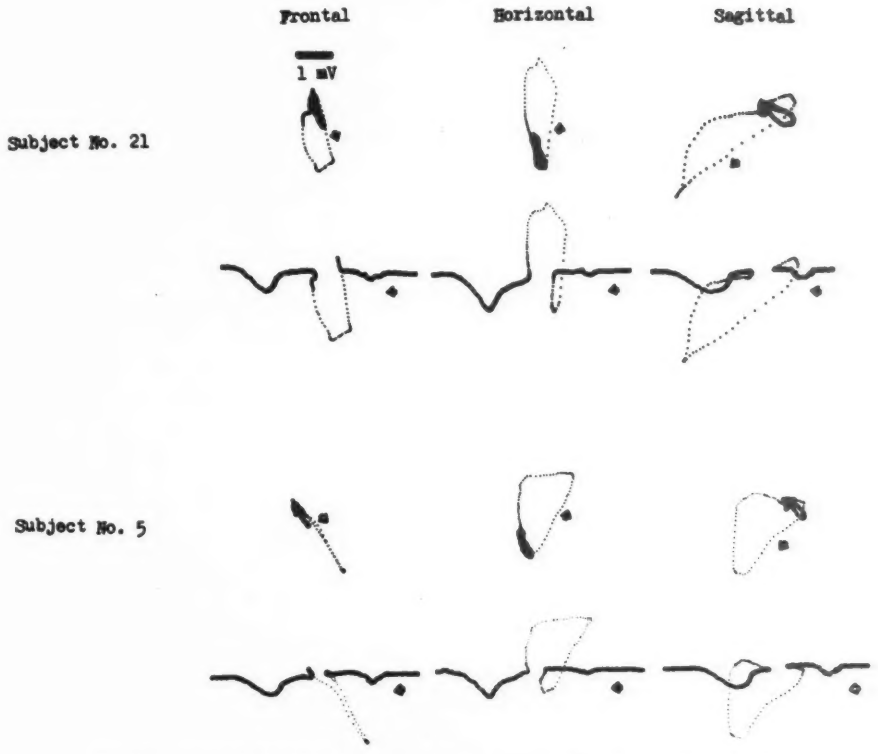


FIG. 10. Typical lead field loops and their corresponding moving-film records.

Static photographs of spatial electrocardiographic loops naturally yield no information concerning the regularity of successive cardiac cycles nor of the time intervals between the atrial and ventricular events of each cycle. This disadvantage can, however, readily be overcome by exposing a moving film during several cycles when the record produced bears some resemblance to a conventional scalar limb lead tracing as seen in figure 10. Not only are the time intervals depicted but such a film has an advantage over the usual electrocardiogram in that the directions of the peaks of the P, QRS, and T components in the 3 planes indicate the spatial orientation of their mean electric axes.

It has long been recognized that different individual hearts may be rotated about any or all 4 anatomic axes, i.e., the anteroposterior, the transverse, and the vertical body axes and the longitudinal axis of the heart itself. Some of these rotations produce qualitative changes in the standard electrocardiographic patterns. In addition, as is well known, enlargement of either ventricle and other cardiac lesions will produce *apparent* changes of heart position, as judged from conventional tracings, by displacing the mean electric axes in space. To distinguish axis deviation due to cardiac defect or pathologic displacement from that due to body constitution or anatomic rotation has always been a difficult problem and to assist in the differentiation resort has been had to mathematical indices such as those of Lewis and Gilder[25] and Jinich.[26] From the present study it would appear that simple inspection of the lead field loops may give considerable assistance in this respect by directly indicating rotation around some of the anatomic axes.

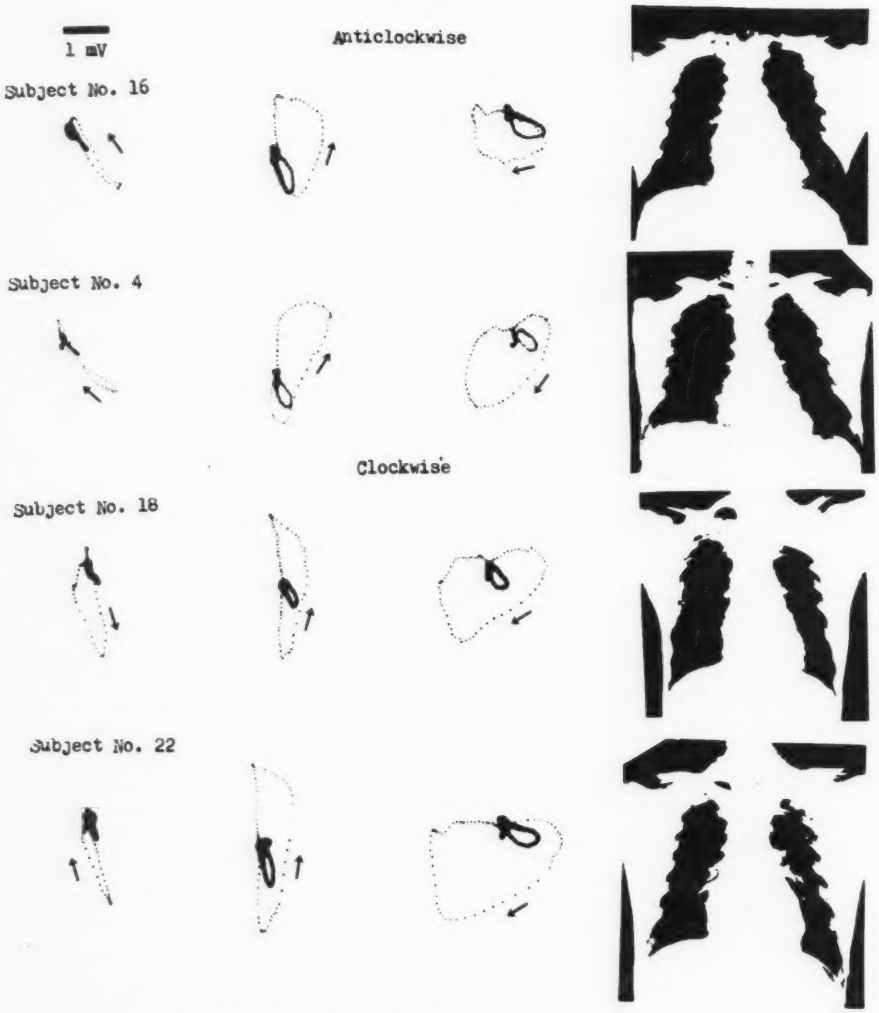


FIG. 11. Lead field loops showing rotation on the anteroposterior body axis.

In figure 11 are shown the loops from 2 pairs of subjects, the upper pair having relatively horizontal and the lower relatively vertical hearts as determined radiologically. Their main QRS loop axes in the frontal plane are near 50° and 80° respectively, which correspond approximately with their anatomic axes. The rotation about the anteroposterior body axis is also suggested by reference to the horizontal plane loops, which are narrower as the heart is more vertical.

Further evidence for close association between the loop axis and anatomic position of the heart can be obtained by observing the changes in loop contour during the inspiratory and expiratory phases of respiration.

Indication of loop rotation around the transverse axis of the body, causing the apex to be placed more dorsally or ventrally than usual, is seen in figure 12 where, in the upper case, evidence of marked posterior tilting of the horizontal and sagittal plane loops is ap

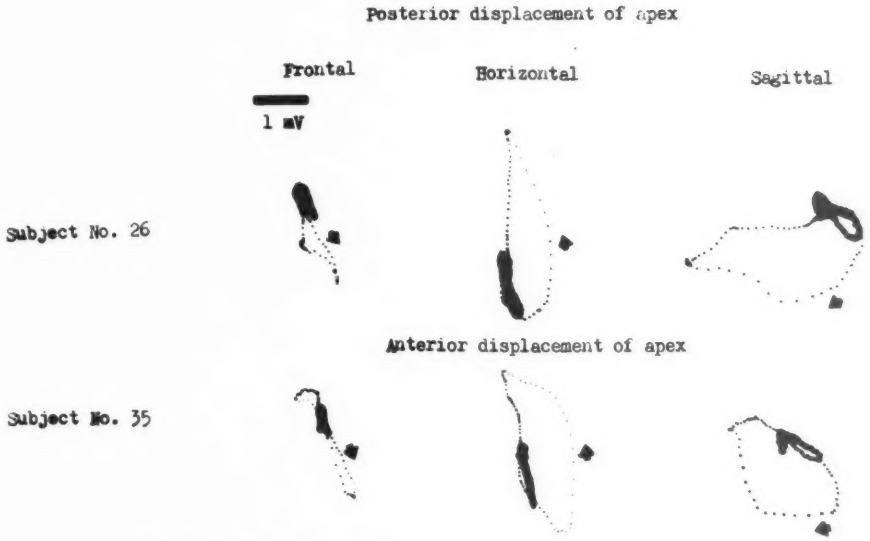


FIG. 12. Lead field loops showing rotation on the transverse body axis.

parent and, in the lower case, the reverse effect. As would be anticipated, the frontal plane loops are not affected. This type of anatomic rotation is difficult to confirm radiologically but we believe that rotation of the loop in this plane probably also reflects changes in anatomic position of the heart.

In addition, the fact that normally the spatial planes of both QRS sÊ and T sÊ are almost perpendicular to the frontal plane of the body and, therefore, project very narrow loops on that plane might be expected to provide evidence of rotation on the heart's longitudinal axis. The frontal plane loop would be widely open and inscribed clockwise in clockwise rotated hearts (when viewed from the cardiac apex) as shown in the top set of tracings in figure 13 and also widely open but inscribed anticlockwise in hearts rotated anticlockwise on their long axes, as in the lowest tracings.

Various criteria have been applied in the past to the conventional bipolar and unipolar limb and chest lead electrocardiograms by which to attempt to characterize the different types of cardiac rotation. In order to determine the effects to be expected on the standard scalar leads from rotation of the lead field loops, a wire model of a typical normal spatial loop system was constructed from which drawings of the projected planar loops were made as the model was rotated around various axes. From the frontal plane drawings, by the usual method of projections on to the Bayley hexagonal reference frame, the expected scalar tracings for the standard bipolar and unipolar limb leads were derived. Similarly, predicted unipolar chest lead patterns were obtained from the projections of the horizontal plane loops on to the appropriate chest reference frame.

The frontal, horizontal, and sagittal plane projections for various rotations of the standard typical lead field loop are shown in figure 14 together with the derived bipolar and unipolar scalar tracings. These predicted patterns are seen to be similar to those actually obtained by the usual clinical 12-lead technic on normal hearts and the variations produced by rotation are those that have previously been accepted as criteria. For example, clockwise rotation around the anatomic transverse axis (as viewed from the left side of the body), thus bringing the cardiac apex anteriorly, increases $Q_2$ and $Q_3$ in these derived tracings, while anticlockwise rotation on the

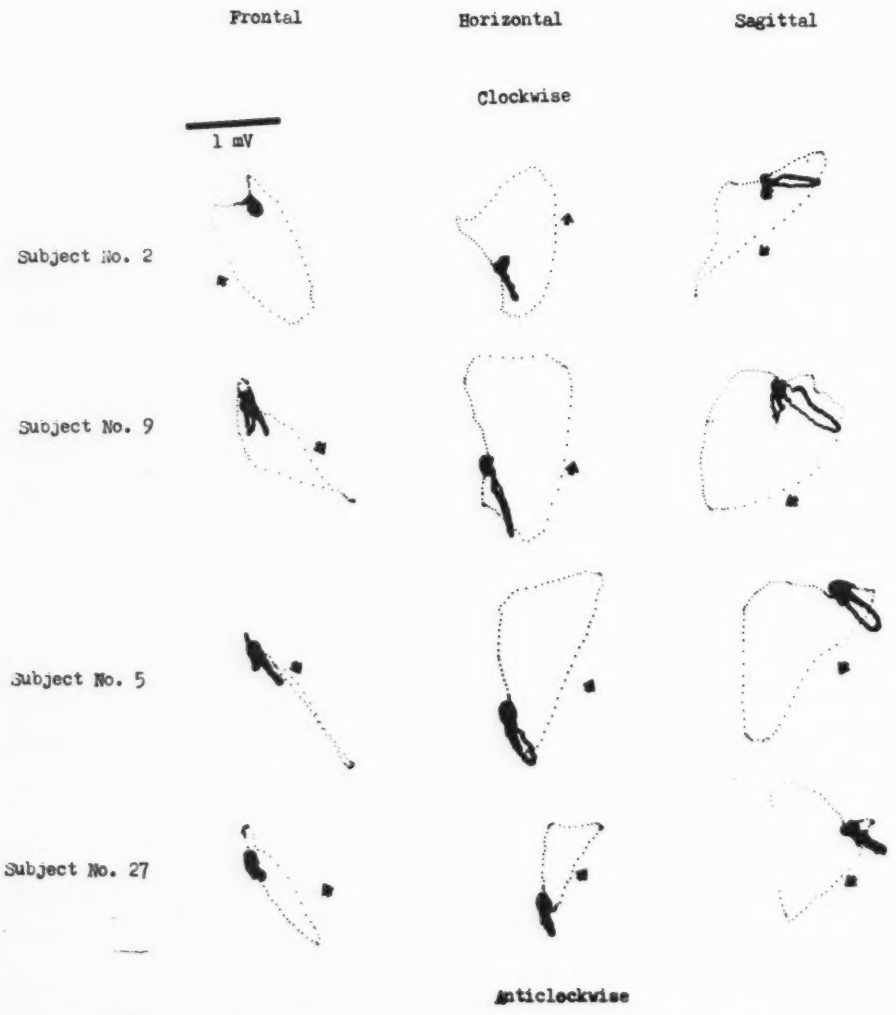


FIG. 13. Lead field loops showing rotation on the longitudinal cardiac axis.

same axis (cardiac apex posteriorly) produces an $S_2$ and $S_3$. These are similar to the changes depicted by Ashman.[27] Also, clockwise rotation of the lead field loop around the heart's longitudinal axis produces an $S_1$ and $Q_3$ as stated by Lepeschkin [28] and a shift to the patient's left of the transitional zone in the chest leads.[29] Longitudinal rotation in an anticlockwise direction gives a $Q_1$ and $S_3$ and a transitional zone shift to the right.

From these findings it would appear that the lead field loops are closely related to the conventional clinical leads and, in fact, any 2 loop projections, together with their moving-film counterparts, yield all the information (and that more readily) that can be obtained from the usual 12-lead procedure. In this respect the loops recorded by the lead field technic are greatly to be preferred to those resulting from the "cube" or "tetrahedron" systems of electrode placement, especially in respect of the horizontal plane. The chest lead patterns predicted by these systems bear little resemblance to those ac-

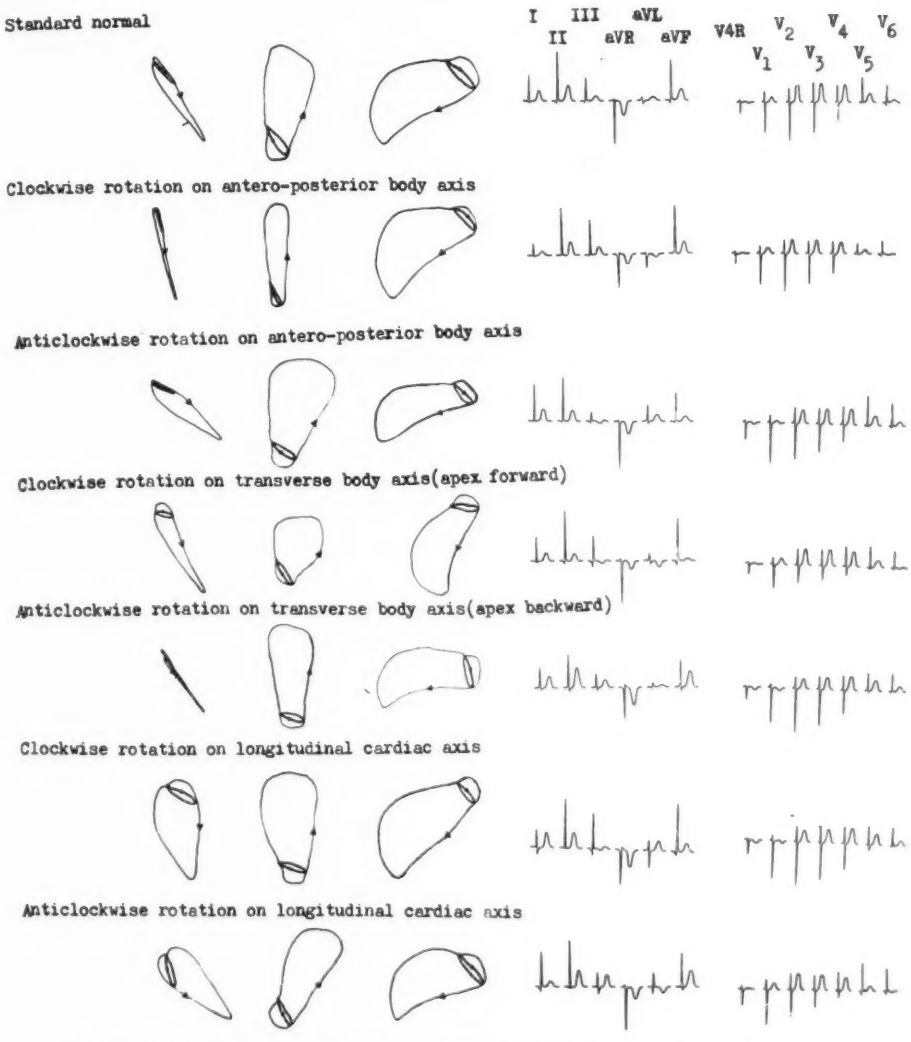
Standard normal
I III aVL
II aVR aVF
V4R V2 V4 V6
V1 V3 V5
Clockwise rotation on antero-posterior body axis
Anticlockwise rotation on antero-posterior body axis
Clockwise rotation on transverse body axis(apex forward)
Anticlockwise rotation on transverse body axis(apex backward)
Clockwise rotation on longitudinal cardiac axis
Anticlockwise rotation on longitudinal cardiac axis

FIG. 14. Standard normal lead field loops showing effects of various types of rotation with predicted limb and chest lead patterns derived by projection of frontal and horizontal planes on to appropriate reference frames.

tually obtained in practice from the same subjects.

Just as inspection of the lead field loops indicates the degree of longitudinal rotation of the heart so the value for $F\hat{A}_{QRS-T}$ can be used for the same purpose. In the normal heart the QRS and T vectors lie in almost the same plane approximately perpendicular to the frontal plane of the body but with QRS directed posteriorly and T anteriorly. Clockwise rotation on this axis will, therefore, increase the manifest angle of QRS and decrease that of T, resulting in an increased positive frontal QRS-T angle. Anticlockwise longitudinal rotation will correspondingly produce a large negative $F\hat{A}_{QRS-T}$.

It is generally recognized that a heart rotated on the anteroposterior body axis usu-

ally manifests some longitudinal rotation in addition. Most vertical hearts show some degree of clockwise and most horizontal hearts some degree of anticlockwise rotation on their long axes.[30] This fact is confirmed by the present findings that demonstrate a close correlation between the frontal plane main axis of the QRS loop and the angle separating that axis from the main axis of the T loop. The larger the axis angle of QRS $\hat{E}$ (frontal), i.e., the more vertical the heart, the larger is the QRS-T angle.

The same result is obtained by using the vectorial values from lead field scalar records. A highly significant positive correlation exists between $F\hat{A}_{QRS}$ and $F\hat{A}_{QRS\text{-}T}$ ($r = +0.69$, $t = 5.8$, $p \ll 0.01$) and an equally significant negative correlation between $F\hat{A}_T$ and $F\hat{A}_{QRS\text{-}T}$ ($r = -0.57$, $t = 4.2$, $p \ll 0.01$). In other words, in a vertical heart the large value for $F\hat{A}_{QRS}$ is associated with a small $F\hat{A}_T$ and hence $F\hat{A}_{QRS\text{-}T}$ is large and positive indicating clockwise longitudinal rotation and in a horizontal heart the small $F\hat{A}_{QRS\text{-}T}$ is associated with a large $F\hat{A}_T$ giving a large negative $F\hat{A}_{QRS\text{-}T}$ indicative of anticlockwise rotation.

In the frontal plane the mean manifest electric axis angle for QRS as determined from the scalar tracings using the lead field electrodes, i.e. 60°, is close to the value usually quoted in the literature as derived from standard limb lead data. However, direct comparison, for each individual in the present series, of the axis angles obtained from lead field tracings and leads I-II and leads I-III (see table 4) shows that there is a significant difference in these angles. The lead field $F\hat{A}_{QRS}$ is less than that obtained from the standard limb leads I-II by 8° ($t = 3.6$, $p < 0.01$). The values for the T vector, on the other hand, are reversed with the lead field axis angle greater than the limb lead angle by an average of 15° ($t = 5.6$, $p < 0.01$). In other words, whereas the QRS-T angle in the frontal plane from the lead field data is very small (+5°) this is apparently increased more than 5-fold by the limb leads which, therefore, appear to "view" the heart as though it were rotated on its longitudinal axis. The manifest ventricular gradient angle is approximately the same by both methods of comparison but the magnitudes of the QRS and T vectors in this plane are some 50 per cent greater by the lead field technic.

The Grishman system gave vectorial angles for the QRS and T axes about 5° smaller than the lead field values as though the whole heart were apparently rotated anticlockwise on its anteroposterior axis. The ventricular gradient angle consequently shifted to the same extent as QRS and T but the frontal plane QRS-T angle remained the same by both methods.

The striking differences between the lead field and Grishman systems in their recording of the horizontal and sagittal planes has already been noted with reference to the orientation of the QRS and T loops. These differences are confirmed by vectorial analysis of the respective scalar tracings. In the lead field horizontal plane the manifest QRS axis is directed posteriorly to the isoelectric point by an angle of 61° (i.e. 299° by the Helm notation) whereas the Grishman system places it anteriorly by 4°. The axis of T is located anteriorly by 70° according to the lead field method and anteriorly by 13° by the Grishman tracings. Although QRS is relatively posterior to T in both cases, the angle separating the 2 vectors is 131° by the lead field system and only 9° by the "cube" method. Correspondingly large differences are shown for the sagittal plane axes. These figures emphasize the insensitivity of the lumbar electrode positions used by Grishman and Scherlis[22] as a sagittal lead.

There is no doubt that for adults of average body build the manifest axis of QRS in the frontal plane lies at about 60°.[31] All the electrode systems previously used for determining this plane yield similar results, and the present findings of 62° and 60° (with standard deviations of about 14) for the main QRS loop axis and $F\hat{A}_{QRS}$ respectively indicate that only about 5 per cent of adults in the population sampled are likely to have

xes differing from that mean by more than =28°. We have not had the opportunity to orrelate all our electric axis data with the eart positions of our subjects as determined adiologically but we have no doubt that the rontal plane angle for the QRS loop and ector would be largely governed by phyique, and hence anatomic position of the eart, as shown by Howard and Gertler.[32]

No such unanimity of opinion exists, however, in regard to the anteroposterior spatial osition of the QRS vector. Conway, Cronvich, and Burch[10] using their tetrahedron ystem found the axis of the QRS sÊ loop o be directed anteriorly by about 10° from he longitudinal axis of the body. By inspection of standard unipolar chest lead calar tracings and selection of the transitional complex, as suggested by Grant and Estes,[33] Urschel and Abbey[34, 35] located the QRS axis as being posterior by about 30° to 60° in electrically intermediate hearts, with the larger angles for the younger individuals. Simonson and Keys[36, 37] by use of a similar technic, also placed the axis posteriorly by about 20° with the angle again tending to be larger in younger men.

Most recently Young, Wolff, and Chatfield[38] have compared the horizontal plane axes for QRS in loops obtained by the Duchosal and Sulzer[39] orthogonal "double cube" electrode system and by the Grishman method. In both cases they found that the main QRS loop axis was directed anteriorly by small angles (6° and 3° respectively). Their mean value for the Grishman loops agrees well with that obtained for comparison with the lead field loops in the present investigation, i.e. 4°.

From all these results it can be concluded that observations based on any of the previously used loop spatial reference frames show an *anterior* displacement of the QRS axis while the technic of transition zone analysis of chest lead tracings places the QRS ector *posteriorly*. The results given by the ad field system, since it uses a multiple midirect chest electrode, would be expected confirm qualitatively the latter findings. In fact, it gives a mean horizontal plane angle posterior to the transverse axis of the body somewhat larger than those previously mentioned, i.e. about 60°, for both the main loop axis and the manifest vector angle.

That the T axis is directed downward, forward and to the left to lie approximately in the same anteroposterior plane as QRS is commonly agreed but the angle of anterior displacement from the transverse line has been variously quoted. Conway et al.[10] found the angle to be about 35°, Grant[40] recorded 3°, Simonson and Keys[36] gave 42° while Young et al.[38] obtained T loop axes by the Duchosal method that were almost transverse.

The lead field method places the T loop axis and $H\hat{A}_T$ much more anteriorly than any of the previously used technics at an angle of about 60° to 70° with the transverse line of the body. This procedure, therefore, confers on the T loop a spatial position roughly similar to the anatomic plane of the heart in the thorax but whether this is a significant observation remains to be determined.

Values previously published for the spatial QRS-T angle have varied with the method employed for its estimation in accordance with the figures quoted above for QRS and T, being very small when estimated by any loop vectorelectrocardiographic technic and larger by chest lead transition zone analysis. Helm and Fowler[41] compared these methods directly on the same subjects and found mean values for spatial QRS-T angles of 18° by the Grishman system, 28° by the "tetrahedron" system, and 43° by chest lead analysis. Our comparative results using the Grishman electrodes gave a mean of +17° but the lead field technic increased this angle to +100°.

As a measure of the mean difference in rate, duration and direction of spread of the electric activity associated with the processes of cardiac depolarization and repolarization, the ventricular gradient is commonly determined. It is computed from the algebraic sum of the scalar areas for QRS and T on a standard lead tracing. If the speed, duration and path of spread of the electric ac-

tivities were identical in the activation and recovery phases, then in any lead the areas of the QRS and T complexes would be equal in magnitude but opposite in sign, their algebraic sum being zero, and no ventricular gradient resulting. The greater the degree by which the recovery process differs in time and direction from that of depolarization, the greater will be the gradient. The fact that a ventricular gradient normally exists is presumably due to the spread of activation being directed along the specialized conducting tissue, whereas repolarization is a slower process pursuing a path wholly or partly independent of the His-Purkinje network. The ventricular gradient, as customarily plotted, is the net resultant vector of QRS and T in any plane and hence its direction is governed by the relative magnitudes, as well as the directions, of the individual QRS and T vectors.

Analysis of the normal human ventricular gradient has been carried out largely by Ashman and his colleagues,[42] who have stated that the spatial angle separating the mean QRS axis and the gradient is approximately 30° with QRS relatively posterior. They also found that the mean (SP)$\bar{A}_G$ was 60° posterior to the anatomic longitudinal axis of the heart as established radiologically. A right-angle in space, therefore, separated the QRS axis from the anatomic position of the heart.

According to our data (see table 2 and fig. 8) using the lead field electrode system, the gradient vector is directed forward in all cases and must, obviously, lie in the same plane as QRS and T. The spatial angle between (SP)$\bar{A}_{QRS}$ and the gradient is, however, considerably greater than Ashman's value, namely 75° (S.D. 19) and the (SP)$\bar{A}_T$ axis lies further anterior by a mean value of 25° (S.D. 10) making a total of 100° between (SP) $\bar{A}_{QRS}$ and (SP)$\bar{A}_T$.

The greater the spatial QRS-T angle the smaller will be the resultant vector of QRS and T (i.e. the spatial magnitude of the ventricular gradient) until, when an angle of 180° is reached, the gradient will be zero if the magnitudes of QRS and T are equal. This statement is borne out by the present data, since a significant negative correlation exists between these 2 quantities ($r = -0.47$, $t = 3.2$, $p < 0.01$). In estimating the net electric difference in time-course of the processes of depolarization and repolarization either the spatial magnitude of the gradient or the spatial QRS-T angle may, therefore, be employed.

Due to the much larger (SP)$\bar{A}_{QRS-T}$ given by the lead field technic as compared with the "cube" system, the magnitude of the gradient is relatively smaller by the former method. By the Grishman system the manifest magnitudes of the gradient in the horizontal and sagittal planes are approximately equal to the sum of the magnitudes of QRS and T because of the small angle between these vectors, but by the lead field method, the spatial magnitudes of T and the ventricular gradient are approximately equal (table 3).

As mentioned earlier, an additional spatial vector, the so-called (SP)$A_{\text{"total" QRS}}$, has been calculated in an attempt to compare the total apparent electric activities associated with the activation and recovery phases of the cardiac cycle. In so far as every instantaneous potential difference recorded by a pair of electrodes placed anywhere on the body surface is a *net* resultant difference, due to numerous instantaneous electric dipoles of various magnitudes oriented in different directions, no method of electrocardiography can be expected to yield much information about the *total* electric activity associated with cardiac contraction. Nevertheless, it appeared of interest to determine the apparent activity actually recorded on the scalar tracings of each plane during depolarization and repolarization by summing arithmetically the areas enclosed by the curve of the QRS complex without regard to sign and to compare this value with the corresponding area under T. In this way a "total" QRS vector for each plane can be plotted analogous to the T vector and its manifest direction and magnitude determined. From

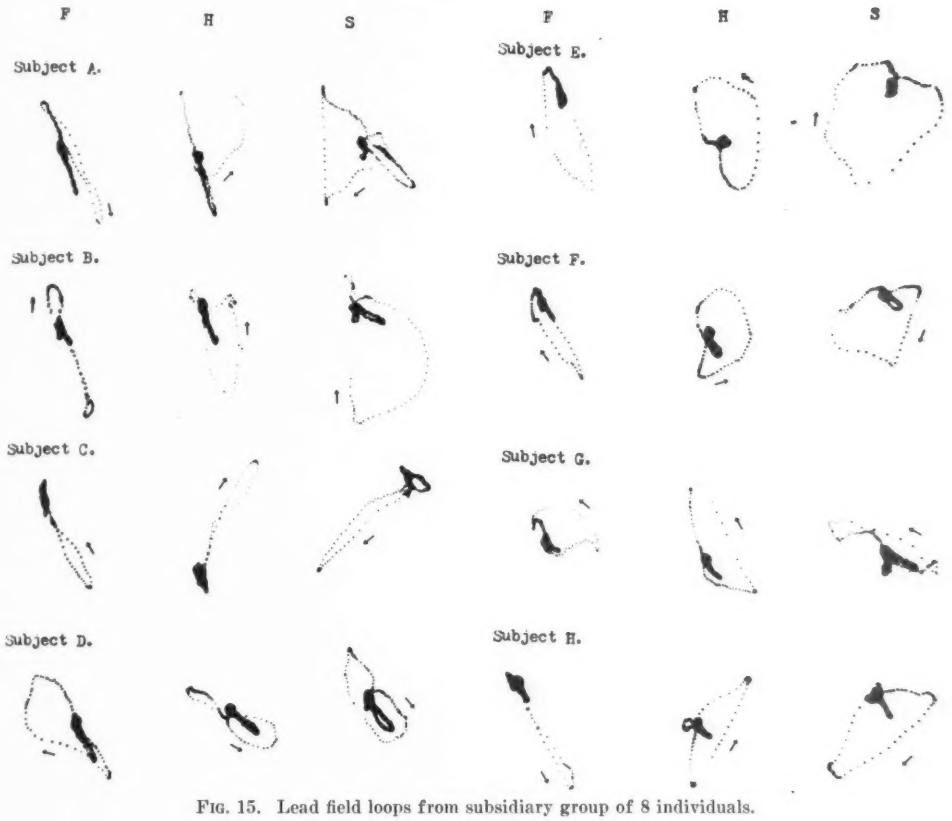


FIG. 15. Lead field loops from subsidiary group of 8 individuals.

these planar values the magnitude of $(SP)A_{\text{"total" QRS}}$ can be estimated in the usual way.

The value of this spatial vector magnitude is related to the corresponding magnitude for QRS obtained by the method of algebraic summation in that for each plane the difference between the arithmetic and algebraic summations for any given complex is obviously equal to twice the area of the downward deflection. The mean ratio of $(SP)A_{\text{"total" QRS}}$ to $(SP)A_{QRS}$ calculated from the individual values given in table 3 is 1.6 (S.D. 0.5) and the difference between the 2 quantities when expressed as a percentage of the larger gives a mean value of 36 (S.D. 16). This figure indicates that normally about 18 per cent of the total electric activity associated with depolarization and recorded as the spatial loop is oriented in a spatial direction opposite from that of the main loop axis. It, therefore, provides an estimate of the proportions lying on either side of the isoelectric point on the planar QRS loop projections.

From table 3 it is seen that the ratios of $(SP)A_T$ to $(SP)A_{\text{"total" QRS}}$ lie fairly closely grouped around a mean of 1.6 (S.D. 0.6) so that the *apparent* electric activity associated with repolarization is some 60 per cent greater than with depolarization. Since these 2 quantities must in fact be equal, it would appear that considerably less "internal neutralization" of instantaneous dipoles occurs during the recovery process, probably due to a more unidirectional sequence of events occupying this period, than is the case during the activation process.

*Subsidiary Group of Eight Individuals*

Each of these cases will be discussed separately in an endeavor to determine the major causes of difference from the mean values of the main group and also to ascertain to what extent various methods of assessment agree in their indications of anatomic rotation of the heart or of any unusual features of the electric activity.

In interpreting the standard and augmented voltage limb leads and unipolar chest leads we have used the criteria of Goldberger[30] and Sodi-Pallares[31] for determination of rotation of the heart around the chief anatomic axes and have compared these findings with the conclusions to be drawn from inspection of the loops shown in figure 15 and the analytical data set out in table 5.

*Subject A.* The heart rate and standard limb lead time intervals for this subject are normal except for a somewhat prolonged P-Q(R) segment occupying 0.10 second. The limb leads demonstrate a marked left axis deviation to −30° (330° by Helm notation) with absence of $Q_1$ and enlarged $S_1$ and $S_3$ which, according to Sodi-Pallares, is indicative of backward displacement of the cardiac apex and anticlockwise rotation on the longitudinal heart axis. The augmented voltage leads, however, would satisfy Goldberger's criteria for marked clockwise rotation rather than anticlockwise. Transition zone analysis of the chest leads suggests an unduly wide QRS-T angle in the horizontal plane.

The loops, on inspection, indicate a normal spatial position for T sÊ but QRS sÊ shows unusually sustained terminal activity above, posterior and to the right of the isoelectric point so that a large spatial angle separates the 2 loops. The frontal plane projection demonstrates a strong anticlockwise longitudinal rotation.

From the main loop axis data QRS sÊ is placed fairly horizontally, with a frontal plane angle of 30°, and an uncommonly large posterior displacement of the loop in the horizontal and sagittal planes to 290° and 164° respectively. Since all the T axes are normal, this leads to a spatial QRS-T angle approximately 30° larger than the mean for the main group of subjects. The frontal plane QRS-T projection of −31° is consistent with anticlockwise rotation on the cardiac longitudinal axis.

Vectorial analysis of the lead field scalar records leads to similar qualitative conclusions but the rotations appear to be exaggerated by this method. A marked left axis deviation is indicated by $F\hat{A}_{QRS}$ of 334° and posterosuperior orientation of the cardiac apex by 186° for $S\hat{A}_{QRS}$. Since the T and ventricular gradient axis angles are normal, the spatial QRS-T angle is very large (+143°) due chiefly to an increased angle between QRS and G. Gross anticlockwise longitudinal rotation is indicated by −81° for $F\hat{A}_{QR3\text{-}T}$.

Comparison of these several methods of assessment points to the tentative conclusion that the pronounced left axis deviation deduced from scalar tracing analysis is, in fact, due to 3 causes that are suggested by scrutiny of the loops, i.e. (1) slight anticlockwise rotation on the anteroposterior body axis, (2) anticlockwise rotation on the cardiac longitudinal axis, and (3) relative left ventricular preponderance giving rise to the slow sustained terminal QRS activity.

*Subject B.* The standard and unipolar limb leads indicate an electrically vertical heart with marked clockwise longitudinal rotation (Goldberger) and the chest leads have RS type complexes at $V_{4R}$ with apparently 2 transitional zones, one between $V_{4R}$ and $V_1$ and the other between $V_2$ and $V_3$. The implication of this latter finding is that QRS activity is directed well anteriorly, which might be associated with relative right ventricular preponderance.

Loop inspection reveals gross anterior displacement of QRS sÊ, the major portion of which lies anterior to the isoelectric point with the terminal part of the loop situated superiorly and to the right. This implies that the loop is less uniplanar in space than in most subjects, the early and late electrical activities appearing to be inscribed at right

angles to each other. T sÊ is slightly more anterosuperior than usual and the spatial angle between the loops is small.

The marked displacement anteriorly of QRS is confirmed by measurement of the main loop axes in the horizontal and sagittal planes where they are located just posterior to the transverse line of the body. The axes for T suggest some anterior and upward displacement and the spatial QRS-T angle is reduced to 63°.

Vector analysis of the lead field scalar tracings gives a QRS axis directed anteriorly by approximately 50° instead of, as in the main group of individuals, posteriorly by 60°. Despite this fact, the values for $\bar{A}_G$ in all 3 planes are relatively unaffected but a small (SP)$\bar{A}_{QRS-T}$ of 41° results, due almost entirely to a great reduction in its QRS-G component. The small spatial QRS-T angle is reflected in the large magnitude (113 mvs) for the ventricular gradient.

The chief conclusion to be drawn at present from these data is that, in addition to a possible slight anterior anatomic displacement of the heart apex, there is a relative right ventricular preponderance that would appear to result from an unusual orientation of left ventricular activity as evidenced by the aberrant terminal portion of the QRS loop.

*Subject C.* The standard and unipolar limb leads are characterized by the complete absence of Q and S deflections and cannot, therefore, be classified according to the Goldberger criteria. The QRS vector from limb lead areas does not differ from that of the main group but the T vector is more vertical by 20° than would be expected.

The frontal plane loop suggests some anticlockwise rotation on the longitudinal axis since QRS sÊ is inscribed anticlockwise and the T loop is more vertical than that of QRS. In the horizontal and sagittal planes the loops are extremely narrow with little anterior activity whatsoever, thus accounting for the absence of Q and S waves in the conventional tracings.

The main loop axis angles support the suggestion of anticlockwise longitudinal rotation but vectorial analysis of the lead field scalar records demonstrates a unique feature in that the spatial magnitude of QRS greatly exceeds that of T and, in consequence, the ventricular gradient is directed posteriorly.

In this case the loops show more clearly than do the ordinary scalar figures that the initial forces are orientated postero-inferiorly rather than, as is usual, anteriorly and the reason for this phenomenon may be an uncommon time-course for the early stages of depolarization.

*Subject D.* The limb leads show RS type complexes in leads I and II, which would conventionally be interpreted as from a heart with a very marked degree of right axis deviation, while the augmented voltage leads satisfy Goldberger's criteria for a vertical heart with strong clockwise longitudinal rotation and backward displacement of the apex. The chest leads again possess 2 transitional zones, one between $V_{4R}$ and $V_1$ and the other at $V_4$.

Vector analysis of standard limb lead areas confirms a gross right axis deviation to 150° and gives a frontal plane QRS-T angle of +108°, which might suggest an extreme clockwise longitudinal rotation.

From the loops it is seen that T sÊ occupies its typical spatial position and that there is no evidence of any marked rotation either on the anteroposterior body axis or the longitudinal cardiac axis. The QRS loop is, however, atypical in that the frontal plane projection has an unusually large component on the returning limb above and to the right of the isoelectric point. This terminal activity gives a figure-of-eight contour to the horizontal plane loop, which would account for the occurrence of 2 transitional zones in the chest leads.

A pronounced right deviation, with the QRS axis oriented anteriorly and to the right, would be inferred from the manifest vectors derived by scalar area analysis of the lead field tracings and, with T showing a slight displacement posteriorly, (SP)$\bar{A}_{QRS-T}$

is large but of opposite sign from usual, since it places QRS relatively anterior to T. The position of the ventricular gradient in space is not much affected by this reversal. The spatial magnitude of the QRS vector, as calculated in the normal manner by algebraic summation of scalar areas, is very small but the value for (SP)A "total" QRS does not differ significantly from the mean for the main group of subjects.

The conclusion to be drawn from these data would appear to be that the apparent right axis deviation is due to an unusual orientation of the electric activity associated with the terminal stages of depolarization and not to right ventricular predominance per se.

*Subject E.* The resting heart rate in this case was 107 and the termination of the T wave was obscured by the commencement of the succeeding prominent P. Goldberger would classify this heart as vertical with marked clockwise longitudinal rotation. The chest leads had a diffuse transitional zone extending from $V_2$ to $V_4$. Limb lead vectorial analysis would suggest right axis deviation to 105° with clockwise longitudinal rotation inferred from a frontal plane QRS-T angle of +51°.

Inspection reveals a normal shaped QRS sÊ lying somewhat vertically with possibly anterior displacement of the apex, but T sÊ appears to be oriented posteriorly instead of, as usual, anteriorly. These findings agree with loop main axis estimations but vectorial analysis of lead field areas indicates only slight posterior displacement of T with a small spatial QRS-T angle.

The conclusion in this case would seem to be that QRS sÊ is well within the range of variation shown by the main group of subjects but difficulty is experienced in making measurements of T areas on scalar records and in characterizing the T loop because of overlapping of an unusually large P loop whose position in space is a little posterior to that of T and hence has the effect of dragging the apparent T loop posteriorly.

*Subject F.* Qualitative assessment of the standard limb leads suggests a fairly vertical electric axis and the chest leads, with a transitional zone between $V_2$ and $V_3$, some anterior displacement of QRS activity. Goldberger would classify the augmented voltage leads as from a vertical heart with moderate clockwise longitudinal rotation and forward position of the apex. Sodi-Pallares, however, would infer an intermediate heart of both anteroposterior and transverse body axes. The standard lead scalar areas would be interpreted as those of a heart slightly more vertical than usual but without rotation on its long axis.

The loops would indicate a heart intermediate on the anteroposterior axis with slight clockwise longitudinal rotation but with a striking excess of initial activity to the right and anteriorly with a loop apex that appears to be displaced forward. These features result in a main loop axis for QRS sÊ about 40° more anterior than expected in most subjects, and vectorial analysis of the lead field tracings accentuates this anterior position. The spatial QRS-T angle is consequently reduced to 46°.

We conclude that the only significant finding in this case is a relative increase in the electric activity associated with the initial phase of depolarization.

*Subject G.* The standard limb and chest leads suggest a very horizontal electric axis with forward displacement of QRS activity. According to Goldberger the voltage leads imply a horizontal heart with marked clockwise longitudinal rotation and backward position of the apex but Sodi-Pallares, on the other hand, would infer a strong anticlockwise rotation on the long axis. Calculation of the axis vectors from limb lead records gives QRS an angle above the horizontal by 22° (338° by Helm notation) and a QRS-T angle of −29°, which is consistent with anticlockwise longitudinal rotation.

The frontal plane QRS sÊ loop occupies an extremely horizontal position with sustained terminal activity and gross anticlockwise rotation on the long axis, since the loop is in-

·ribed anticlockwise. These features are also pparent from the horizontal and sagittal lane projections. There are, in addition, ıore prominent irregularities in loop contour ıan are generally seen.

The main loop axis data confirm the gross nticlockwise rotation by an angle of −89° for $\hat{A}_{QRS-T}$ and the lead field scalar areas place QRS almost exactly horizontal in the fron-al plane with a large negative QRS-T angle. The relative positions of the QRS and T axes ı space, however, remain completely normal with 100° for (SP)$\hat{A}_{QRS-T}$.

These findings could all be explained on the basis of a fairly typical QRS loop with extreme anticlockwise longitudinal and anteroposterior rotations and, therefore, probably due largely to an exaggerated horizontal anatomic position of the heart.

*Subject H.* A vertical axis is indicated by the standard leads with a normal transition zone in the chest leads. Goldberger analysis would characterize this heart as vertical with moderate clockwise rotation on the long axis and forward displacement of the apex. By Sodi-Pallares it would be labeled as vertical with no longitudinal rotation.

The loops show no appreciable rotation on the longitudinal axis but a greater proportion of QRS sÊ is inscribed anterior to the isoelectric point than in most individuals. The main QRS loop axis is, therefore, placed anteriorly rather than posteriorly and, with the T loop less anterior than usual, the spatial angle between the loops becomes very small (+8°). A similar though less marked result is obtained from the lead field scalar area vectors.

It is concluded that in this case the only noteworthy variation from the majority of subjects is a relative excess of initial QRS activity directed anteriorly.

These 8 cases demonstrate the wide range of variability in electric activity that may be recorded from clinically normal hearts and emphasize the fact that marked divergence of configuration and orientation of the spatial QRS loop from the most common type must be recognized in assessing the normality of any given electrocardiogram. Whether these differences are due to atypical conduction pathways, intrinsic variability of myocardial cellular responses to depolarization, or other factors remains to be determined. Even in these individuals, however, the spatial T loops did not differ fundamentally in shape or position from the mean of the main group of subjects, suggesting that the repolarization process is a more constant phenomenon than depolarization.

## Conclusions

Recently, in a review of the evolution of our knowledge about the heart, White[43] has stated, "vectorcardiography is beginning to be introduced in a useful way, although there is still much to be done in its appraisal . . ." This is undoubtedly true but it should be coupled with the proviso that spatial electrocardiography can only be expected to add significantly to present knowledge and to rationalize the diffuse and largely empirical mass of existing data concerning the electric activity of the heart if adequate attention is paid to the choice of theoretically satisfactory bipolar leads. Johnston[44] has summed up the situation by saying, "If three leads or lead systems can be devised that will yield entirely satisfactory orthogonal components (i.e. transverse, vertical and sagittal) of cardiac electromotive forces these leads would not only be ideal for vectorcardiography but would provide a scheme by means of which most of the data now requiring at least nine leads could be recorded in three electrocardiograms. The writer believes that the lead field concept points to methods for accomplishing this desirable end."

The evidence obtained in the present study convinces us that the lead field technic described above is a simple, rapid, and practical procedure involving little more discomfort to the patient than conventional electrocardiography and yielding in 3 scalar patterns or 2 planar loops more accurate information in a more readily assimilable form than can be derived from the usual 12-lead tracings. The lead field loops more faithfully represent the

resultant electric activity associated with the cardiac cycle than do those of any previously described system of vectorcardiography.

The anatomic position of the heart and its spatial rotations are indicated by the loop planar projections; the speed and direction of activation and any preponderance of early or late phases of depolarization are immediately apparent.

We conclude that the T loop from the normal heart occupies a more constant spatial position than does QRS sÊ, which may vary considerably in shape, position, and regularity of contour, and that the apparent electric activities associated with depolarization and repolarization are more nearly equal in magnitude and opposite in spatial orientation than has generally been recognized.

The standard criteria of Goldberger and others for classifying the rotations of a given heart by reference to limb and chest lead scalar tracings would appear to be fairly satisfactory as long as the QRS loop in space is uniplanar and of average shape, but discrepancies in interpretation of the scalar patterns arise when the shape of the loop differs from the mean to any marked extent.

## Summary

A survey has been made of the spatial resultant cardiac electromotive forces of 47 normal male medical students using electrode placements chosen to satisfy the requirements of the lead field concept of McFee and Johnston. For registration of the anteroposterior component a new type of multiple chest electrode has been described.

Thirty-nine of the subjects gave results that were closely similar, while the remaining 8 differed to varying degrees from the main group.

Typical planar QRS and T loops for the main group are presented and their main axes are shown to lie infero-posteriorly to the left and infero-anteriorly to the left respectively. The mean spatial angle separating the axes of the 2 loops is +83°.

The lead field loops are compared with those obtained from the same subjects by 3 current methods of spatial vectorcardiography and attention is drawn to the increased sagittal component manifest by the new procedure. The correlation between the standard limb and chest lead tracings predicted from the frontal and horizontal planar loops and those actually recorded by conventional electrocardiography is demonstrated.

Vectorial analysis of the lead field scalar tracing areas has been carried out for all subjects and the electric axes for QRS, T, and the ventricular gradient have been determined and compared with those obtained from standard limb leads and the "cube" system of electrode placement. The calculated axes are similar to those derived from loop axis estimation but the mean spatial QRS-T angle is increased slightly to +100°.

In an attempt to compare the apparent magnitudes of the electric activities associated with the depolarization and repolarization processes an additional spatial vector magnitude, $(SP)A_{\text{"total" QRS}}$, has been calculated and its ratio to $(SP)A_T$ determined.

The variations shown by the 8 individuals from the means of the main group have been discussed separately and suggestions made to account for the differences.

## Acknowledgment

We wish to record our gratitude to Professor J. M. Peterson and Dr. William Phillips for their encouragement; to the Medical Research Council for a grant to cover the cost of the camera; to our senior technicians, W. L. Barry and D. H. Brown without whose skilled assistance the cardioscope could not have been constructed; to Dr. G. Grant and Dr. G. Hinde for clinical and radiological advice respectively, and especially to the students for their willing cooperation.

## Summario in Interlingua

Esseva effectuate un investigation del resultantes spatial del fortias electromotori cardiac de 47 normal studentes mascule de medicina, con le uso de un placiamento del electrodos que satisfaceva le requirimentos del concepto de campo de derivation de McFee e Johnston. Pro le registration del componente antero-posterior un nove typo de multiple electrodo thoracic esseva empleate.

Trenta-nove del subjectos monstrava resultatos que esseva multo simile. In le resto de 8 subjectos le resultatos differeva ab le gruppo principal a varie grados.

Es presentate typic ansas planar QRS e T pro le gruppo principal. Es signalate que le axes principal jace infero-posteriormente verso le sinistra e infero-anteriormente verso le sinistra, respectivemente. Le valor medie del angulo spatial que separa le axes del duo ansas es +83 grados.

Le ansas de campo de derivation es comparate con le ansas obtenite ab le mesme subjectos per 3 currente methodos de vectocardiographia spatial. Es signalate le augmentate componente sagittal que es manifeste per le nove procedura. Le correlation inter le registrationes a derivation standard de extremitate e thorace, predicite de un latere super le base del frontal e horizontal ansas planar e observate del altere latere in ver registrationes per electrocardiographia conventional es demonstrate.

Un analyse vectorial del areas de registration scalar a campo de derivation esseva effectuate pro omne le subjectos, e le axes electric pro QRS, T, e le gradiente ventricular esseva determinate e comparate con illos obtenite per derivationes standard e per le systema "cubic" del placiamento de electrodos. Le axes calculate es simile a illos derivate ab le estimation del axes principal de ansa, sed le valor medie del angulo spatial de QRS e T es augmentate levemente a +100 grados.

In le effortio de comparar le magnitudes apparente del activitate electric que es associate con le processos de dispolarisation e de repolarisation, un magnitude additional de vector spatial– (SP) $A_{QRS\text{"total"}}$ esseva calculate, e le proportion inter illo e (SP)$A_T$ esseva determinate.

Le deviationes del 8 individuos ab le valores medie del gruppo major es discutite separatemente. Possibile explicationes es offerite.

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# ERRATUM

On pages 1104-1106 of the June issue (article by Hubert V. Pipberger) the amplitude data in tables 2 and 3 have to be divided by a constant factor of 1.75 for the correction of an error made in the computation.

# CLINICAL PROGRESS

## Cardiovascular Reactions to Symbolic Stimuli

*By* STEWART WOLF, M.D.

SYMBOLIC stimuli are those that derive their force not from their intrinsic qualities but from their significance to the individual. Cardiovascular symptoms, disability, and death may result from alterations in a wide variety of bodily mechanisms that regulate cardiovascular function. The bodily structures responsible for these alterations include the hypothalamus and other parts of the brain, the pituitary gland and its subsidiaries, the thyroid and adrenal glands, the kidney, and possibly other viscera, such as the liver, the heart, and the blood vessels themselves. There is a growing body of evidence that all these structures are connected with, and capable of, reacting to excitation in the interpretive areas of the brain.

It is likely that a variety of cardiovascular disturbances occur in relation to stressful life experiences from day to day and even many times a day without producing discomfort. Only when pronounced or sustained do such changes become clinically important.

### DIRECT EFFECTS OF STRESS

In the category of disorders directly attributable to a stressful situation may be classified "voodoo death" or sudden death in healthy individuals as seen from time to time in our own culture. There has been some difference of opinion among investigators as to whether such effects were attributable to massive sympathetic or to parasympathetic discharges. Cannon[1] took the former view but more recently the experiments of Richter[2] indicate that heart slowing as a result of vagal stimuli may be the important factor with the ultimate production of ventricular fibrillation. Richter was able to produce such vagal effects experimentally in rats who were placed in a tank from which they could not escape and in which they were made to swim indefinitely. It is interesting that survival among these rats was greatly reduced when their orienting mustache hairs were cut off, thus putting them into an even more unaccustomed "terrifying" and presumably hopeless situation. Richter further noted that wild rats did not survive this ordeal as well as did the domesticated rats, who had been accustomed over the generations to the arduous buffetings of the experimental laboratory. A comparable observation in a human being was made by Fuqua[3] who was on duty in a field hospital during the war in Korea. He was examining a marine with symptoms of influenza and, after listening to the breath sounds with his stethoscope, Fuqua said "now stop breathing" as he began to listen to the heart. With that the marine's heart suddenly stopped and he fell to the floor pulseless and remained asystole for approximately 1 minute with no real effective pulsation for at least 2 minutes. Further contributory evidence in human beings was gathered by Furman[4] in the course of the examining of the hearts of soldiers at the time of induction into the military service. The long line of recruits came for their cardiovascular examination immediately after a blood sampling syringe was withdrawn from their veins. He thus caught many subjects almost in the process of fainting and indeed caught some of them as they were keeling

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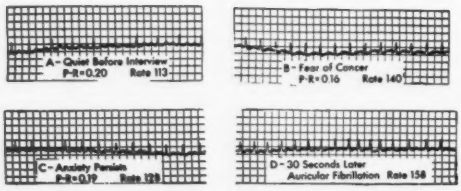
A - Quiet Before Interview
P-R=0.20 Rate 113
B - Fear of Cancer
P-R=0.16 Rate 140
C - Anxiety Persists
P-R=0.17 Rate 129
D - 30 Seconds Later
Auricular Fibrillation Rate 158

FIG. 1. Sudden appearance of atrial fibrillation during a stressful interview.

over and falling to the floor. Prompt examination revealed pulse rates in the low 40s and blood pressure that was almost unobtainable. Although many recruits showed tachycardia, those who fainted displayed uniformly a vagal pattern. The basis for such reactions is not clear but certainly anxiety is too simple a psychodynamic explanation for these facts. The soldiers found themselves in many anxiety-producing situations from time to time without fainting. Whether or not there is a special, subtle, and largely unconscious threatening significance in having a pierced skin has never been adequately explained. The experience of snake bite may be somewhat akin to needling in a doctor's office. In any case, herpetologists and those familiar with snakes and snake bites hold that about 85 per cent of sudden deaths that follow snake bite cannot be explained on the basis of the quantity of venom inoculated. Sometimes sudden deaths occur following the bite of nonpoisonous snakes and often a poisonous snake responsible for the bite is not large enough to deliver a lethal dose of venom. Likewise many instances of drowning may be attributable to excessive vagal effects on the heart rather than to asphyxia. According to Kunkel,[5] water polo players who are prevented from getting to the surface of the water in competition develop a technic of losing consciousness so that they sink to the bottom of the pool whence they are quickly extracted and readily revived to continue on with the game.

The occurrence of various arrhythmias in association with emotional stress is familiar to most clinicians. It is not widely recognized, however, that such disorders as atrial

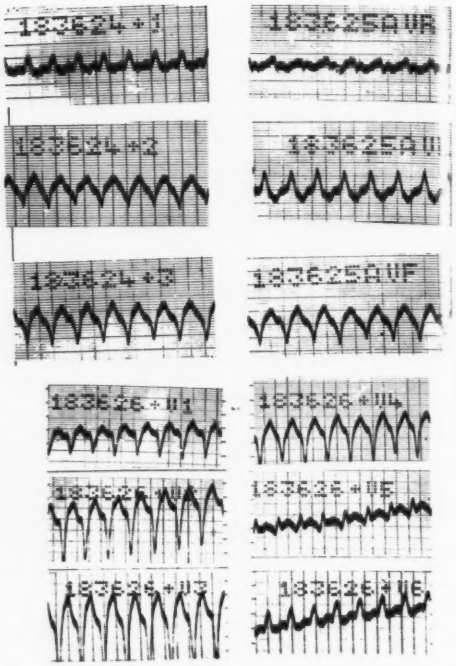

FIG. 2. Ventricular tachycardia occurring under stress in an apparently healthy man without evidence of structural heart disease.

fibrillation and ventricular tachycardia may be induced in apparently normal hearts by circumstances that have a stressful meaning to the individual. Such changes are illustrated in figures 1 and 2 and are reported in detail in a separate publication.[6]

### STRESS AS AN AGGRAVATING FACTOR

The second general category of disturbances attributable to stress are those that contribute to or aggravate disability in patients with already damaged hearts or compromised circulations. Among such mechanisms that are susceptible to alteration by stimuli emanating from the interpretive areas of the brain are, in addition to rate and rhythm, cardiac output, peripheral resistance, and hence the mechanisms that govern the work of the heart. Electrocardiographic changes, especially involving the T waves and similar to those induced by ex-

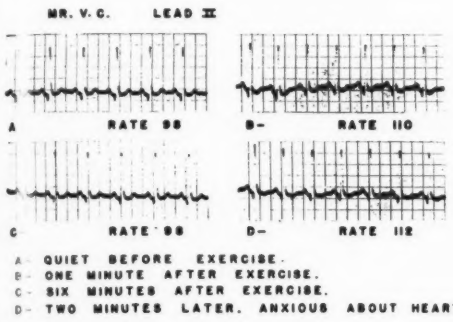
MR. V. C. LEAD II
A RATE 98
B- RATE 110
C RATE 98
D- RATE 112
A- QUIET BEFORE EXERCISE.
B- ONE MINUTE AFTER EXERCISE.
C- SIX MINUTES AFTER EXERCISE.
D- TWO MINUTES LATER. ANXIOUS ABOUT HEART

FIG. 3. Marked depression of T waves in lead II of electrocardiogram. Essentially the same change was observed after exercise and during discussion of a stressful topic. In this instance the T-wave changes may be related to the changes in rate.

cise may be seen, as shown in figure 3 and discussed elsewhere in a separate publication.[7] In this instance the T-wave changes may be related to the changes in rate. Grabiel and co-workers[8] were able to produce a wide variety of electrocardiographic changes in response to sudden startling stimuli such as the shooting of a gun in a laboratory. Schottstaedt and associates[9, 10] have shown on the one hand a substantial diuresis of sodium and water, and on the other a significant retention under differing circumstances of stress occurring in healthy subjects as well as in those with impaired cardiac function.

### SYSTEMIC HYPERTENSION

It is an old observation, and very easily confirmed, that patients with essential hypertension, and normal subjects as well, display an increase in arterial pressure when brought into certain situations involving threats to their personal security. The pertinence of these responses to the initial causation or ultimate perpetuation of sustained arterial hypertension, however, is not established. The investigator who studies hypertension is handicapped by the lack of relationship between height of the blood pressure and the presence or absence of symptoms and the lack of uniformity and predictability of the natural course of the disease.

It has been shown, however, with appropriate documentation, that hemodynamic changes productive of elevated arterial pressure, reduced renal blood flow, and increased blood viscosity occur as a part of an individual's adaptation to problems and challenges in his daily life.[6, 11] Special attention has been directed to 2 contrasting patterns of hemodynamic adjustment that occur alike in hypertensive and normotensive individuals under stress. One pattern appears to be identical with the "exercise" pattern, which is characterized by an increase in blood pressure attributable to a rise in stroke volume without elevation of peripheral vascular resistance. The other pattern resembles that encountered in injury or hemorrhage. It is characterized by an increase in blood pressure attributable to an elevation in peripheral resistance without a rise in stroke volume. When observed during interviews that deal with pertinent personal conflicts, the "exercise" pattern was manifest when emotional disturbance was relatively overt, while the "high resistance" pattern was more often encountered with a calm exterior and evidence of suppression or repression of emotion.

In essential hypertension there occurs a sustained increase in peripheral resistance without a rise in stroke volume. There was not, however, a significant difference between hypertensive and normotensive subjects in reactions to short-term stressful situations. Neither was there any correlation between an indvidual's response to interview and his reaction during a cold pressor test or between the type of vascular reaction to stress and the degree of vascular damage as reflected by the eyegrounds, heart size, or kidney function.

Further experimental studies have shown that the renal vasculature shares in the circulatory response to stressful events in the life situation. A decrease in effective renal plasma flow and an increase in filtration fraction occurred in both hypertensive and normotensive subjects during a discussion of pertinent personal conflicts.

It was particularly notable that the mechanisms of the vascular apparatus responsible for raising the blood pressure in response to symbolic stimuli were not impaired by thoracolumbar or even "total" sympathectomy. Either the "exercise" or "high resistance" pattern might still occur, although no longer was there evidence of associated reduction in renal blood flow. It is conceivable that the loss of renal vasoconstrictor activity may protect the kidneys and thereby have a salutary effect on the course of essential hypertension. Perhaps, it may be a factor in the apparent increased survival of sympathectomized patients even without notable reduction of arterial pressure.

The significance of all these findings is not clear but there is nothing incompatible with the view that the life adjustments in individuals with essential hypertension involve initially renal ischemia which may in turn set off a variety of endocrine and other humoral mechanisms with the ultimate development of irreversible tissue damage. In any case it is clear that stressful life experiences are sufficiently prominent among stimuli to elevated arterial pressure to warrant their serious consideration in the clinical management of patients with essential hypertension. The evidence of emotional restraint and the calm exterior often displayed by these patients make it necessary for the physician to exercise special diligence and skill in uncovering meaningful life experiences and the attitudes and reactions associated with them.

A study of personality adjustment among the patients with hypertension did not delineate any characteristic personality "type," but yielded strikingly similar data as regards values, attitudes, and way of life. By and large the hypertensive subjects had grown up feeling the need to excel but at the same time to avoid conflict or too vigorous self-assertion. These strivings, often opposed as they were, led frequently to dilemmas and were manifest, by wary, tentative, and noncommittal attitudes with respect to important interpersonal relations and major endeavors in life.

In the author's series 12 per cent of hypertensive patients under psychotherapy lost all evidences of hypertension. These individuals appeared to have developed a more confident and relaxed approach to life, a more optimistic outlook, and an improved capacity for self-assertion.

It is probable that most adaptive functions of the cardiovascular system are responsive to stimuli that owe their force to their special significance to the individual. Thus, like disorders of the gastrointestinal tract, cardiovascular disorders can probably be contributed to or perhaps actually initiated by stressful life situations as well as by antigens, microorganisms, nutritional, climactic, and traumatic stresses. The alterations in renal blood flow that have been induced in human subjects, both normotensive and hypertensive, by introducing stressful topics for discussion are probably germane to the problem of essential hypertension.[6] Such stressful interviews have also been shown to induce an increase in blood viscosity and shortening of the blood clotting time as measured in vitro.[11] Thus the circulatory adaptations that may accompany emotional stress may have far reaching metabolic effects and may compromise circulatory efficiency in those with already existing cardiovascular damage. There has even been speculation concerning the possibility that the stresses and strains of daily life may enter into the mechanism responsible for coronary arteriosclerosis. Currently there is an interesting possibility that the concentration of lipids in the blood may be relevant to the pathogenesis of atherosclerosis and coronary artery disease. The studies of Groover,[12] Friedman and Rosenmann[13] and Hammarsten and his associates[14] have given evidence that the lipid-regulating mechanisms are responsive to situational stresses. The latter studies were undertaken on 12 men ranging in age from 30 to 70. They all had well-documented evidence of myocardial infarction. These individuals were followed at weekly intervals with chemical determination of serum cholesterol, lipid phosphorus, and lipoproteins as estimated by the ultra-

centrifugal technic. At the same time, each subject kept a written record of everything he ate each day at meals and between meals. The dietary records were later analyzed and roughly quantitated in terms of caloric content and proportion of fat, carbohydrate, and protein in the diet. In addition, the subjects were weighed each week and were carefully interviewed concerning events of the week and their attitudes and reactions to potentially stressful situations. Following the interview the investigator recorded a judgment concerning the presence or absence of significant stress during the week and an estimate of its degree. These data were, of course, gathered and recorded entirely separately from the chemical measurements. Later correlation showed that unusually high cholesterol concentration, more than 15 per cent above the mean, for any individual in the study correlated with a high degree of significance with periods that had been separately judged as especially stressful. Similar correlation was found in the lipoproteins of the $S_f$ 0-12 and $S_f$ 12-20 fractions.

### Physiologic Response "As If"

Most individuals who see a cinder in the eye of another begin themselves to lacrimate as if there were a cinder in their own eye. A hungry person who sees or even thinks about a delicious meal may salivate and may indeed pour forth increased amounts of acid gastric juice. Another example of the physiologic response "as if" was observed in a study of cardiac output in response to exercise.[6] It soon became evident that it was unnecessary to exercise the subjects in order to induce the characteristic hemodynamic adjustments. They could readily be called forth by the mere discussion of exercise.

Energy requirements for particularly vigorous exertion are presumably supplied by fat mobilization and metabolism. In a large group of untrained adult males ranging in age from 22 to 51 years, Clarke and Balke[15] found that total serum cholesterol rose *during exercise* and remained high throughout the exercise interval but quickly fell to resting levels after cessation of exercise. Steiger and associates[16] have identified a lipid-mobilizing factor, which is secreted by the pituitary gland in response to starvation, muscular exertion, and to situational stresses. It thus appears that the lipid mobilizing mechanism may be responsive to impulses that emanate from the interpretive areas of the brain and that derive from stimuli which owe their force to their meaning, a physiologic response "as if" great muscular effort were required.

The studies of Hammarsten and his associates[14] indicated that the patient with coronary artery disease was oriented to life along the line of effort, of doing things "the hard way." The patients placed an especially high value on doing things "on their own," and being solely responsible for their activities and experiences. Like Sisyphus they appeared to be continually carrying a burden and never quite getting it to the top of the hill or the resting place. The occurrence of coronary attacks appeared to correlate with periods when the individuals were carrying an especially heavy emotional load. It may be that in these individuals the mechanisms that govern the concentration of the serum lipid are brought into play in the face of a demand for effort that is figurative as well as literal. Such a theory would tend to explain the favorable results reported by those cardiologists who actually encouraged their coronary patients to engage in vigorous muscular effort.

At the present time the inference is a speculative one that hypercholesteremia in some instances may represent a stress reaction with the individual reacting to a threatening life situation inappropriately, as if great muscular effort were being called for. Notwithstanding such speculation, it is evident that the work of the heart cannot be estimated with any degree of accuracy with reference to the amount of exertion actually undertaken. If the subject is "in training," cardiovascular efficiency will be such that a relatively great load may be carried with a minimum

of work. On the other hand, in training or not, the heart may be called upon to work hard with the subject sitting or lying while contemplating consciously or unconsciously some troublesome personal problem.

Much of the confusion concerning the role of life stress in disease derives from failure to distinguish between cause and mechanism. All mechanisms are perforce organic and at the same time functional, since they involve the functions of units of the body's equipment. Causes, on the other hand, are likely to derive from the outside, often from noxious stimuli in the environment. The causes, which may be multiple, activate the pathogenic mechanisms and produce bodily disorders and disease. The ability of symbolic stresses to participate in the activation of disease mechanisms depends upon the fact that most bodily organs are connected with and responsive to impulses reaching them via autonomic and endocrine pathways from the highest integrative centers of the nervous system, the interpretive areas of the brain.

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# ABSTRACTS

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## ATHEROSCLEROSIS

**Wilens, S. L., and Gallo, G.: The Effect of Chlorpromazine on Arterial Lipid Deposition in Rabbits After Cholesterol Feeding.** Arch. Path. **64**: 570 (Nov.), 1957.

Rabbits were permitted to eat normal diets for 10 weeks after an initial 10-week period of cholesterol feeding. Blood cholesterol levels returned to normal, and visceral deposits of lipid were resorbed during this time. Arterial lipid deposits, however, persisted and may even have been more extensive than if the rabbits were killed at the end of the cholesterol-feeding period. Chlorpromazine administered to rabbits after a 10-week period of cholesterol feeding accelerated the rate of fall of blood cholesterol levels. A moderate reduction in extent of arterial deposit was found in rabbits receiving chlorpromazine during the post-cholesterol-feeding period, as compared to control rabbits which did not receive the drug. This difference is attributed to the more rapid fall in blood cholesterol following cholesterol feeding in the chlorpromazine-treated group, rather than to resorption of previously formed lipid deposits.

MAXWELL

**Sm ch, E. B.: Lipoprotein Patterns in Myocardial I farction. Relationship Between the Com- nents Identified by Paper Electrophoresis a d in the Ultracentrifuge.** Lancet **2**: 910 (Nov. 9 , 1957.

S rum lipoproteins were studied by paper ele rophoresis and ultracentrifuge analysis in no al subjects, patients with established acute my ardial infarction, with old infarcts or angi or with peripheral arterial disease. A new component, the pre $\beta$-lipid, never present in large amount in normal subjects, was absent in 80 per cent of women and 83 per cent of men under 30, but was present in a moderate amount in 67 per cent of men over 50. In comparable age groups, the prevalence of a moderate pre $\beta$-lipid band is the same for patients with clinical symptoms of peripheral arteriosclerosis, for patients with angina and old infarcts, and for those without symptoms. A large pre $\beta$-lipid band is often associated with definite evidence of coronary artery disease. Ninety per cent of patients with fresh myocardial infarction show some abnormality of lipids and 50 per cent of these abnormalities are gross. After infarction the pre $\beta$-lipid increases, reaching a maximum 3½ to 5 weeks after the attack.

KURLAND

**Gordon, H., Lewis, B., Eales, L., and Brock, J. F.: Dietary Fat and Cholesterol Metabolism. Faecal Elimination of Bile Acids and Other Lipids.** Lancet **2**: 1299 (Dec. 28), 1957.

Saturated and unsaturated fats have been fed to subjects for up to 60 days and the action of these fats on serum cholesterol level was correlated with the fecal elimination of fat, neutral sterols, and, in particular, bile acids. The ingestion of sunflower-seed oil lowered and hydrogenated coconut oil raised the serum cholesterol level and these effects were sustained for 60 days. In men fed large amounts of hydrogenated coconut fat, the addition of an equal amount of sunflower-seed oil led to a substantial fall in the serum cholesterol. Heating sunflower-seed oil as in domestic cooking did not change its action. Following administration of sunflower-seed oil, normal fat absorption was maintained for long

periods. The fall in serum cholesterol was accompanied by a slight increase of fecal neutral sterols that generally tended to follow the total amount of fecal fat, but there was considerable increase of fecal bile acids. The latter represent a true increase in the excretion of bile acids and not a failure of reabsorption nor is it a nonspecific cholagogic action of fat for it does not appear after feeding hydrogenated coconut fat.

KURLAND

**Keys, A., Anderson, J. T., and Grande, F.: Prediction of Serum-Cholesterol Responses of Man to Changes in Fats in the Diet.** Lancet **2:** 959 (Nov. 16), 1957.

Groups of men between the ages of 30 to 55 were studied in caloric balance with a constant rate of energy expenditure in carefully controlled dietary experiments on each of 2 to 6 diets in which 9 to 44 per cent of calories were derived from fat. Fats studied included butter-fat, hydrogenated coconut oil, olive oil, cotton-seed oil, corn oil, sunflower-seed oil, safflower oil, fish oil, and mixed food fats. Prediction equations were developed for the conditions of the experiments. The data indicate that the saturated fatty acids, at least those larger than 10 carbons, have about twice as much effect in raising the serum cholesterol level as the cholesterol-depressing effect of an equal amount of polyethenoids or linoleic acid. The evidence does not support the concept that a deficiency of essential fatty acids produces the high cholesterol level of our society. It suggests that effective correction involves a decreased intake of common fats as well as substitution of fats high in polyethenoid fatty acids.

KURLAND

**Hallberg, O. E.: Sudden Deafness and Its Relation to Atherosclerosis.** J.A.M.A. **165:** 1649 (Nov. 30), 1957.

A study of 178 cases of sudden deafness of obscure origin led to the classification of 89 cases of vascular origin, probably from a vascular accident. Thirty per cent of the 89 cases were in the 20- to 30-year age group. Since less than 4 per cent of angina pectoris cases fall within this age group, the 2 conditions differ markedly in age distribution. Four of these patients whose blood was tested for cholesterol, fatty acids, and total lipids gave high normal or supernormal values suggestive of atherosclerosis. The results of treatment in these cases have all been disappointing. The most common cause of sudden deafness is a vascular accident involving the blood supply to the cochlea, equilibratory labyrinth, or both. Evidence points to the fact that patients so affected are more susceptible than the average to the development of other types of vascular accidents later in life. For this reason, in addition to a careful examination of the ear, a complete general examination (possibly including blood lipid studies), and a neurologic examination are indicated for patients who suddenly become deaf.

KITCHELL

## BLOOD COAGULATION AND THROMBOEMBOLISM

**Ensor, R. E., and Peters, H. R.: Experience with the Anticoagulant, Marcumar.** Ann. Int. Med. **47:** 731 (Oct.), 1957.

A comparison of Marcumar with Dicumarol and Cumopyran in 288 long-term out-patients with coronary disease demonstrated the superiority of Marcumar, even when given to the most difficult patients in the series. An additional spot check of 161 out-patients with phlebitis and coronary disease verified the satisfactory levels obtained with Marcumar. It is believed, then, that the latter drug is superior to the other long-acting anticoagulants. Marcumar by its prolonged duration of action gives a more stable and satisfactory type of curve. Its advantages far overshadow its initial delayed action. In this respect it is stressed that any patient requiring urgent anticoagulation receive heparin rather than short-acting anticoagulants. In this entire series there was no death due to hemorrhage. The drug was administered to 400 postoperative patients in order to prevent postoperative thromboembolic complications. In this group there were only 3 instances of minimal hemorrhage. In 91 postoperative bowel, stomach, and gallbladder cases, despite their known liability to anticoagulant hemorrhage, Marcumar was given but with extreme caution. One patient with moderate gastrointestinal hemorrhage responded to blood transfusion and vitamin $K_1$ intravenously. Anticoagulants were then stopped in this patient. Ten days after discontinuance, the patient died and autopsy revealed massive pulmonary embolism. It was observed that in postoperative prophylaxis in bowel, stomach, and gallbladder cases, there was no instance of thromboembolism while the patient was under therapy. Since the goal in anticoagulant therapy is adequate depression of blood prothrombin and a constant maintenance of a stable level, Marcumar appears to be the ideal oral anticoagulant.

WENDKOS

**Fairbairn, J. F., II, and Estes, J. E.: Clinical Experience with 3-(1-Phenylpropyl)-4-hydroxycoumarin.** Proc. Staff Meet. Mayo Clin. **32:** 342 (June 26), 1957.

Comparison of 90 patients who received Marcumar (3-1-phenylpropyl)-4-hydroxycoumarin as

anticoagulant drug with 100 patients who received Dicumarol did not reveal major differences in regard to toxicity or ease of maintaining therapeutic levels of plasma prothrombin activity. Therapeutic levels of plasma prothrombin activity were not attained as rapidly in patients who received Marcumar as in those who received Dicumarol combined initially with Tromexan as a "priming" agent. Plasma prothrombin activity achieved a therapeutic level within 48 hours in almost 100 per cent of the patients who received Dicumarol and Tromexan. In only 73 per cent of the patients who received Marcumar was this level attained within 48 hours. There were no significant differences between the 2 groups regarding frequency of excessive reduction in the plasma prothrombin activity. No adverse drug reactions to Marcumar or Dicumarol were observed. The response of reduced plasma prothrombin activity to administration of vitamin $K_1$ showed that this drug was an antagonist to the anticoagulant action of marcumar. A single dose of vitamin $K_1$ did not return the plasma prothrombin activity to normal within 48 hours on 15 separate occasions. When prompt return of plasma prothrombin activity to normal is necessary, multiple doses may be required. The necessity for this can be decided on the basis of serial determinations of prothrombin time. There were 5 instances of bleeding during therapy with Marcumar, 2 of which were considered to be of major consequence (hematemesis and hemopneumothorax). Two deaths occurred during Marcumar therapy, neither of which could be attributed to use of the anticoagulant drug.

SIMON

**McDonald, L., and Edgill, M.: Coagulability of the Blood in Ischaemic Heart-Disease.** Lancet 2: 457 (Sept. 7), 1957.

The coagulability of the blood was studied in 48 patients with angina pectoris without recent infarction and in 48 matched controls. In 1 group studies were also controlled by a double-blind technic. A statistically significant difference was found between patients and controls in thromboplastin generation, platelet stickiness, Russell's viper venom prothrombin time, and fibrinogen content. No significant difference was found in clotting time, factor VII content of plasma and serum or platelet counts. The evidence indicates increased coagulability of blood in patients with ischemic heart disease.

KURLAND

**Da , W. A.: Ligation of the Inferior Vena Cava f r Thromboembolism.** Surgery **43**: 24 (Jan.), 1 58.

a background upon which he might present his experiences with 16 patients who underwent inferior vena cava ligation in the management of thromboembolism, the author reviews some of the current opinions concerning the efficacy of anticoagulant drug therapy and superficial vein ligation in the therapy and prevention of this disorder. In addition, he reviews all of the papers by American surgeons reporting on results obtained in groups of 5 or more patients who have had caval ligation to control thromboembolism. Anticoagulant drug therapy is generally advocated for venous thrombosis and pulmonary embolism. Ligation of the inferior vena cava is indicated when: (a) there is thrombosis above the level of the superficial femoral vein; (b) there is failure of adequate anticoagulant therapy; (c) some contraindication to anticoagulants exists, and (d) certain rare indications exist such as septic pelvic phlebitis and phlegmasia cerulea dolens. The operative technic and certain anomalies of the vena cava are discussed. There were no operative mortality and no further embolism following caval ligation. All but 2 patients exhibited some degree of leg edema in the early postoperative period, but it was not a great problem after a few days. Of the 11 patients followed beyond 10 months, there are 4 with edema or ulcer and 2 who had pain on exertion during damp weather. The leg results, although far from normal, were nevertheless considered good in that 14 of the 16 patients who cooperated faithfully in postoperative management, returned to their occupations and were in no sense invalids. Careful postoperative management of the legs is of great importance and the details of this management are discussed. Special emphasis is placed upon the prevention of edema of the legs.

BROTHERS

## CONGENITAL ANOMALIES

**Brotmacher, L., and Campbell, M.: The Natural History of Ventricular Septal Defect.** Brit. Heart J. **20**: 97 (Jan.), 1958.

The authors describe the natural history of ventricular septal defect based upon 75 persons who were catheterized and an additional 100 clinically diagnosed cases to determine the age and sex difference. Of the 75, 23 had central cyanosis, usually of gradual onset. More than half of these 23 were over 20 years of age. Of the 175, more than three fourths were under 20 and only 10 per cent of the acyanotic were over this age. The cyanotic cases decreased with age, but the incidence of cyanosis remained practically unchanged. Only 6 per cent of a combined series of 400 were over 40 years of age. Females more frequently had normal pulmonary artery pressures, were acyanotic, and over 20 years of age. Clinically, a harsh systolic murmur and

thrill at the left fourth space, absence of electrocardiographic evidence of extreme right ventricular hypertrophy, and presence of radiologic evidence of left ventricular enlargement favored ventricular over atrial septal defect. Pulmonary regurgitation was well tolerated but aortic regurgitation was not. Heart size depended primarily upon the magnitude of the present or past left to right shunt but the heart could become smaller with the development of a right to left shunt. A small defect with a shunt of less than 2.5 liters a minute permitted a normal right ventricular pressure, but a larger defect permitted left ventricular pressure to be transmitted to the right ventricle so that the pressure differential was small. As the pulmonary resistance and systolic pulmonary pressure increased with age, the left to right shunt reversed. This reversal may be aided by an increase in the size of the defect. For these reasons, Roger's and Eisenmenger's syndrome have outlived their usefulness. Ventricular septal defects are classified as follows: (1) small defects with a small left-to-right shunt only (up to 3 or perhaps 3 to 5 liters a minute); (2) larger defects with a left-to-right shunt of 4 to 5 liters a minute, still with a normal pulmonary arterial pressure; (3) larger defects with pulmonary hypertension that is hyperkinetic with a left-to-right shunt only; (4) larger defects, still with a left-to-right shunt only and with pulmonary hypertension that is due to increased pulmonary arteriolar resistance (above 3 units); (5) larger defects with a right-to-left shunt also. Here the aorta is functionally overriding; it may always have been anatomically overriding or may have become so.

SOLOFF

**Goodwin, J. F.: Pregnancy and Coarctation of the Aorta.** Lancet **1**: 16 (Jan. 4), 1958.

The hazards of coaretation of the aorta and the effects of pregnancy on this lesion are evaluated both from published reports of 123 cases and personal experience with 13 patients. The mortality of pregnancy complicated by coaretation is 9.5 per cent which is in contrast to that of 29 per cent in a published combined series of 94 cases. The 2 most common single causes of death were aortic rupture and aortic aneurysm. The absence of evidence suggesting a tendency to medial necrosis of the aorta in pregnancy and the similarity of mortality rates of coaretation with and without pregnancy suggest that pregnancy does not confer an added risk to patients with uncomplicated coaretation. Consequently, patients with uncomplicated coaretation should be allowed to go to term and be delivered by the vaginal route with a shortened second stage. Careful watch should be maintained for aortic infection and aortic aneurysm. After delivery, aortic resection should be advised and subsequent pregnancies can probably be contemplated without anxiety. When serious heart disease is present, it should be diagnosed early and pregnancy terminated before the twentieth week. If it has progressed further than that, the management should be that of any patient with heart disease in pregnancy.

KURLAND

**Grosse-Brockhoff, F., Loogen, F., and Wolter, H. H.: Analysis of Atrial Pressure Curves in the Determination of the Size of Atrial Septal Defects.** Ztschr. Kreislaufforsch. **46**: 874 (Nov.), 1957.

In large atrial septal defects the second or V wave in the left atrium is considerably lower than normal, while this wave in the right atrium is slightly higher, so that their amplitude and configuration are nearly identical in both atria. The first or A wave remains much higher in the left than in the right atrium. If during withdrawal of the catheter from the left into the right atrium it becomes evident that the left atrial curve has a V wave exceeding 10 mm. Hg and definitely higher than in the right atrium, the septal defect is usually not significant enough to warrant operation. If at the same time, the blood gas analysis shows a considerable left-to-right shunt, the presence of aberrant pulmonary veins is almost certain. This was true in 18 per cent of all patients with atrial septal defect.

LEPESCHKIN

**Giraud, G., Latour, H., Puech, P., and Roujon, J.: Anatomic Forms and Diagnostic Peculiarities of the Persistent Common Atrio-ventricular Canal.** Arch. mal. coeur **50**: 909, (Oct.), 1957.

Defective development of the dorsal and ventral endocardial cushions leads to 3 types of persistent common atrioventricular canal. The incomplete form shows atrial septal defect of the ostium primum type, accompanied by a split septal leaflet of the mitral valve. In the intermediate form the septal leaflet of the tricuspid valve is also split. The complete form shows continuous atrial and ventricular septal defect with absence of the septal leaflets of the mitral and tricuspid valves. In 6 personal cases diagnosis was confirmed at autopsy, while in 3 additional cases it was possible because of direct passage of the catheter into the left ventricle (confirmed by means of intracardial leads). In all patients the electrocardiogram showed complete or incomplete right bundle branch block with a mean QRS axis between -80° and -115°; this pattern

as not found in any other type of congenital art disease, and is probably due to bilateral incomplete bundle branch block. A "P congenitale" attern and a prolonged P-R interval are common, but appear also in other types of congenital heart disease. The septal defect usually leads a left-to-right shunt and increase in pulmony flow; location of the defect more to the left, ith tricuspid hypoplasia, was found in only 2 tients. In these patients the left ventricular pertrophy and strain pattern was found in the ecordial leads. Pulmonary hypertension is more mmon in the complete than in the incomplete rms; when it is sufficient to reverse the shunt constitutes a contraindication against operative treatment.

LEPESCHKIN

**Holzmann, M., and Kieser, C.: Thirty-four Year Survival in an Incomplete Common Truncus Arteriosus.** Cardiologia **31**: 36 (Fasc. 1), 1957.

In a 34-year-old woman with cyanotic congenital heart disease, catheterization data suggested a transposition complex with a common ventricle. Autopsy revealed a common origin of the main pulmonary artery and aorta from a large vessel overriding a ventricular septal defect. From the embryologic viewpoint this malformation corresponded to an arrest in an early stage of development of the aortic-pulmonary septum and was termed by the author "incomplete truncus arteriosus communis." The radiologic findings in particular prominence of the pulmonary segment, were helpful in the distinction of this condition from a complete truncus. The case demonstrates that exceptionally patients with a common trunk may survive to adult life.

PICK

**Heintzen, P., and Rohwedder, H. J.: A Contribution to the Clinical Picture of Congenital Diverticulum of the Ventricle.** Ztschr. Kreislaufforsch. **46**: 817 (Nov.), 1957.

A 6-year-old boy showed 2 pulsation maxima in the apical region, a loud high-pitched systolic murmur and a very short protodiastolic murmur. Fluoroscopy disclosed a round shadow, showing systolic outward pulsation, at the cardiac apex. Angiocardiography through the cardiac catheter caused this shadow to be filled with dye. The electrocardiogram showed a notched R wave in lead $V_3$, a very tall R wave in $V_4$, and a low notched T wave in these leads. Since no definite signs of myocardial ischemia were found, it was concluded that the aneurysm did not result from myocardial infarction secondary to aberrant origin of a coronary artery, but corresponded to a congenital diverticulum.

LEPESCHKIN

**Scebat, L., Voridis, E., Renais, J., and Lenégre, J.: Pulmonary Arterial Hypertension in Interatrial, Interventricular and Aortico-pulmonary Communications.** Arch. mal. coeur **50**: 801 (Sept.), 1957.

Hemodynamic studies by means of cardiac catheterization disclosed that pulmonary arterial hypertension was constant and attained high values in all cases where blood from the left side of the heart reached the right side at a high "injection pressure" (e.g. large aortico-pulmonary and interventricular communications, 82 patients). It was considered to be due to pulmonary arterial constriction, partly as a response to sudden stretching and partly as a reflex caused by the oxygen needs of the body. Later irreversible arterial changes developed. In cases where the injection pressure was low (e.g. atrial septal defect, 65 patients) pulmonary hypertension was inconstant and moderate; it usually developed as a result of left ventricular failure or increased pulmonary resistance due to chronic bronchopneumonitis, thrombosis, or primary disease of the pulmonary artery.

LEPESCHKIN

**Gilman, R. A., Skowron, C. A. R., Musser, B. G., and Bailey, C. P.: Partial Anomalous Venous Drainage.** Am. J. Surg. **94**: 688 (Nov.), 1957.

Partial anomalous venous drainage may exist as an isolated entity, but more frequently it is accompanied by an atrial septal defect. For this reason, any surgeon faced with the prospect of correcting an atrial septal defect must be prepared to recognize and treat any co-existent anomalous pulmonary veins. Twenty-two patients with this anomaly have been operated upon by the authors. There were 4 postoperative deaths, but all 18 survivors, with follow-up of 3 to 36 months, have shown improvement. These patients were divided into 5 well-defined types. The method of surgical correction for each type is presented. The technic of atrioseptopexy, or some modification thereof, was utilized in most of the patients.

BROTHERS

## CONGESTIVE HEART FAILURE

**Decortis, A.: A Study of the Plasma Volume and Serus Proteins in Cardiac Decomposition.** Acta Cardiol. **12**: 240 (Fasc. 3), 1957.

The composition of serum proteins was studied by the electrophoretic method in 20 patients with heart failure. In 80 per cent low albumin values were found, only partly compensated by an increased concentration of $\beta$ and $\gamma$ globulins resulting in hypoproteinemia. Edema fluid contained very little protein, and although its elec-

trophoretic pattern corresponded to that of the serum, the albumin/globulin ratio was higher. In the plasma of patients with heart failure the total amount of proteins was higher than in normal individuals due to an elevation of the globulins, but there was no correlation between the increase of plasma volume and hypoalbuminemia. The lowest concentrations of albumin were found in arteriosclerotic and hypertensive patients and to lesser degrees in patients with mitral disease and cor pulmonale. The hypoalbuminemia could not be ascribed totally to dilution of the albumin fraction within an increased plasma volume but seemed to depend on some other factors responsible for depletion of protein stores of the organism. The author advocates ample supply of dietary proteins to patients with heart failure.

PICK

## ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

**Abildskov, J. A., Hisey, B. L., and Ingerson, W. E.: The Magnitude and Orientation of Ventricular Excitation Vectors in the Normal Heart and Following Myocardial Infarction.** Am. Heart J. 55: 104 (Jan.), 1958.

In 44 normal subjects and 20 patients with myocardial infarction recordings of the heart's electric activity as curves of spatial magnitude, frontal plane orientation, and orientation about an anteroposterior axis were obtained. Both the equilateral tetrahedron reference system and the precordial lead system of Frank were used. In comparing these new records in the 2 groups of patients the information known to be clinically important in standard and unipolar limb leads of the electrocardiogram was found to be present in easily recognized form. In addition, the normal and abnormal records also showed significant differences in several parameters which could not be easily evaluated from the conventional electrocardiogram or vectorcardiogram. These latter points are described and commented upon.

SAGALL

**Miquel, C., Sodi-Pallares, D., Cisneros, F., Pileggi, F., Medrano, G. A., and Bisteni A.: Right Bundle Branch Block and Right Ventricular Hypertrophy. Electrocardiographic and Vectorcardiographic Diagnosis.** Am. J. Cardiol. 1: 57 (Jan.), 1958.

Seven cardiac patients underwent thorough clinical study including cardiac catheterization and right ventricular cavitary electrocardiographic recordings. Three with mitral stenosis had Rs or R complexes in $V_1$ indicative of right ventricular hypertrophy. In 2 of the 3 there was slurring of the upstroke of the R waves, and the intracavitary tracing showed an Rs with a delay in the intrinsic deflection beyond 0.035 second, both of which findings suggested a degree of block additionally. The vector loops in the horizontal plane were projected anteriorly and rotated clockwise in all 3. Four patients with other heart conditions had M-type QRS complexes in the right precordial leads consistent with right bundle branch block, which appeared to be incomplete in 3. Intracavitary tracings showed RS, rsr' S, or rS complexes with delay of the intrinsic deflections of 0.03 to 0.06 second. The horizontal plane vectors were inscribed clockwise or counterclockwise, and not all were slurred.

The horizontal plane vectorcardiogram of a dog whose right bundle branch had been cut showed displacement of the loop to the right and anteriorly with clockwise rotation through the major portion of its development and a slurred counterclockwise segment terminally. The authors therefore believe that there is no loop rotation that might be considered specific for right bundle-branch block.

ROGERS

**Fox, I. J., and Wood, E. H.: Use of Methylene Blue as an Indicator for Arterial Dilution Curves in the Study of Heart Disease.** J. Lab. & Clin. Med. 50: 598 (Oct.), 1957.

The contours of dilution curves recorded simultaneously at the radial artery and at the ears following successive injections of equal doses of Evans blue and methylene blue were studied in 12 healthy subjects, 28 patients with congenital heart disease, and 9 patients with acquired heart disease. Methylene blue in doses required for diagnostic purposes did not produce discoloration of the skin, as may occur following use of Evans blue. In equal doses methylene blue produced a peak deflection which was approximately double that following injection of Evans blue; however, the systemic recirculation peak was diminished or absent. Methylene blue was found to be largely lost from the blood stream on its first circulation and could be detected in bloodless ear tissue within seconds after its injection. Determinations of dye content in bloodless (pressurized) ear tissue 2.5 minutes after intravenous injection of 0.2 (0.1 to 0.3) mg. per kg. of Evans blue and of methylene blue revealed appreciable quantities of methylene blue but no detectable Evans blue in the tissue at this time. In vitro experiments revealed rapid (approximately 50 per cent) diminution in spectral absorption within 2 minutes after the mixing of methylene blue dye and whole

blood. The apparent concentration of dye in the mixture then remained approximately stable for the duration of the observations (30 minutes). A preciable apparent loss of methylene blue from the blood stream during its first passage through the pulmonary circulation was demonstrated. In patients with left-to-right shunts a similar degree of correlation was demonstrated between the degree of disproportionate prolongation of the disappearance slope of Evans blue and methylene blue dilution curves and the magnitude of the shunt as determined by cardiac catheterization. Methylene blue can be used in a similar fashion to Evans blue dye for the detection and localization of right-to-left shunts. Loss of methylene blue in the dye-blood mixture traversing the lungs may result in an overestimation of the magnitude of right-to-left shunts when this indicator is used. It is concluded that methylene blue is a valuable adjunct to Evans blue for use as an indicator for recording of selective dye-dilution curves during diagnostic cardiac catheterization.

MAXWELL

**Esch, I., Heeger, H., and Saiko, G.: On the Genesis of the Third Heart Sound.** Ztschr. Kreislaufforsch. **46**: 917 (Dec.), 1957.

In phonocardiograms of 35 persons aged 7 to 28 years, who showed a physiologic third heart sound appearing 0.12 to 0.14 second after the beginning of the second heart sound, this sound was visible at frequency ranges of 35 and 70 cycles per second in all instances. In 5 persons it was visible also at 140 cycles, and in 1 of these it was no longer visible in this range after 2 years. Because of its high-frequency components, the third heart sound is attributed to stretching of the atrioventricular valves and the papillary muscles during rapid ventricular filling. In 13 patients with a pathologic third heart sound the frequency range was about the same as in normal persons. The third sound in this instance is attributed to transient closure of the atrioventricular valves at the end of the rapid filling phase.

LEPESCHKIN

**Gärtner, W., and Schaefer, H.: Theory and Clinical Usefulness of the Electrocardiographic Ventricular Gradient.** Arch. Kreislaufforsch. **27**: 83 (Oct.), 1957.

Of 1,075 patients, 113 with clinically normal hearts had a frontal plane ventricular gradient ranging from 16 to 120 micro-volt-seconds, but the ratio of the gradient to the QRS area averaged 2 and varied only between 1.33 and 3. This ratio was less than 1.5 in only 6 per cent of normal persons, but in 72 per cent of those with definitely abnormal hearts. In aortic and mitral disease the ratios had about the same values as in normal individuals. In hypertension, 77 per cent of persons with a ratio less than 1.33 had impaired cardiac function (100 per cent if persons with left axis deviation exceeding –45 per cent were excluded). In left bundle-branch block a gradient less than 40 or 0.63 of the QRS area was found only in definitely impaired cardiac function; in right bundle branch block this was the case for a gradient less than 25. When the QRS is wide, an exact correlation of the gradient to the QRS area is possible only if the normal QRS area is known. In normal hearts the gradient of extrasystoles is not significantly different from that of normal beats. In normal hearts the angle of the gradient ($\alpha$G) is about 10° greater than 0.72 of the QRS angle ($\alpha$QRS) if the latter is positive; if $\alpha$QRS is negative, $\alpha$G can have any value greater than $\alpha$QRS. Abnormal hearts show no great differences from normal hearts. The relation between G and QRS warrants the conclusion that G has one component dependent on that of QRS; impaired cardiac function causes a decrease predominantly of the first component. This component may depend on anatomic factors such as thickness of ventricular wall, type of contraction, oxygen supply, temperature gradients, and metabolic peculiarities; all these factors would be expected to become more uniform with dilatation of the heart. The second component may depend on factors such as diameter of myocardial cells and conduction velocity.

LEPESCHKIN

**Scebat, L., Renais, J., Meeus-Bithe, L. and Lenègre, J.: Accidents, Indications and Contraindications of Catheterizations of Right Cardiac Cavities.** Arch. mal. coeur **50**: 943, (Oct.), 1957.

Of 1,364 catheterizations, severe venous spasm occurred in 0.6 per cent, usually when local anesthesia was inadequate. In 1 patient the tip of a catheter remained in the pulmonary artery branch; it was very well tolerated. In 1 patient formation of a knot required operative removal from the axillary vein. Pyrogenic shock (at first 25 per cent) could be practically eliminated by soaking the catheter in 10 per cent oxygen for an hour. Transient vago-vasal syncope occurred in 3.2 per cent, usually after longer explorations. Arrhythmias appeared in 95 per cent, but persisted in only 0.5 per cent; right bundle-branch block appeared in 2 per cent. Pulmonary edema appeared in 2.6 per cent, only in left cardiac disease; it could be controlled by resting or sitting up. A local inflammatory reaction occurred in 30 per cent, but required antibiotics in only 1.5 per cent, especially in the presence of streptococcal infection among the personnel. Fourteen

patients complained of pleuritic pain attributable to a small pulmonary infarction. Death attributable to catheterization occurred in 12 of 2,175 catheterizations. In 1 patient it was due to hemopericardium after ventricular perforation, in 1 to hematoma in the coronary sinus region, leading to cardiac standstill. In these patients the operators were overconfident and insufficiently experienced. In 2 patients standstill occurred during anesthesia or during intrapulmonary injection of protoveratrine. In 1 patient it was due to hemopericardium without anatomic perforation; in 1, coma and death occurred after injection of ether into the pulmonary artery. In 4, death followed pyrogenic shock; and in 2, pulmonary edema or shock appeared after 6 to 7 days. Absolute contraindications to catheterization are Osler's endocarditis, active rheumatism, recent myocardial infarction, ventricular tachycardia, or polytopic extrasystoles. Catheterization should be avoided in patients with marked anxiety, fever, frequent extrasystoles, or severe cardiac failure, and in left bundle-branch block, since right bundle-branch block would transform it into complete block.

LEPESCHKIN

**Giraud, G., Latour, H., Puech, P., Mimran, R., and Hertault, J.: Catheterization and Angiography of the Ductus Arteriosus Retrogradely from the Aorta (Percutaneous Femoral Method.** Arch. mal. coeur **50**: 969 (Nov.), 1957.

A 52-year-old man showed a systolic murmur continuing into the diastole and a "diastolic overload of the left ventricle" in the electrocardiogram. Right cardiac catheterization showed a left-to-right shunt, but the persistent ductus could not be demonstrated directly. Retrograde catheterization from the femoral artery was therefore carried out, using the percutaneous technic developed for visualization of renal arteries. The polyethylene catheter easily entered the ductus from the aorta, and angiocardiography of the pulmonary artery could be carried out through it.

LEPESCHKIN

**Gadermann, E., and Jungmann, H.: Pathologic Physiology of the Arterial Pulse in Different Circulatory Diseases. III: The Arterial Pulse in Large Central Aneurysms.** Ztschr. Kreislaufforsch. **46**: 838 (Nov.), 1957.

In 5 patients with large pulsating aneurysms of the thoracic or abdominal aorta the femoral pulse was characteristic only of the advanced age of the patients, showing reduced dierotic elevation and appearance of the incisura in the femoral pulse. No signs of an increased elastic reservoir were present. In 1 patient with aneurysm of the iliac artery the femoral pulse on the side of the aneurysm showed an increased dierotic elevation, but no reduction in amplitude compared to the normal side. Registration of pulses is accordingly of no diagnostic significance in aortic aneurysms.

LEPESCHKIN

**Jungmann, H., and Gadermann, E.: Pathologic Physiology of the Arterial Pulse in Different Circulatory Diseases. II: The Arterial Pulse in Aortic Isthmic Stenosis.** Ztschr. Kreislaufforsch. **46**: 835 (Nov.), 1957.

In 4 patients with isthmic stenosis of the aorta the optically registered carotid pulse showed a straight diastolic descent, while the femoral pulse showed also a straight, slow ascent, leading to a triangular configuration. The dierotic and predierotic notches were absent. The dorsalis pedis pulse showed these changes much less clearly. The characteristic form appeared also in dogs during compression of the aortic arch. The pulse-wave velocity between the carotid and femoral arteries was normal for the age of the patients. The changes in the pulse configuration were diagnostically significant, but might not be apparent if electric pulse registration with an A-C amplifier were used.

LEPESCHKIN

**Wasserburger, R. H., and Brown, J. H.: $AV_R$—An Index of Right Ventricular Preponderance: Correlation of QRS Patterns in $AV_R$ and the Right Precordial Leads with the Ventricular Workload Ratio.** Am. Heart J. **55**: 33 (Jan.), 1958.

In order to establish electrocardiographic criteria for the diagnosis of right ventricular predominance applicable to infants, children, and adults and also to depict the value of lead $aV_R$ in assessing the right ventricular workload, the electrocardiographic patterns of 245 patients with established right ventricular hypertension or an increase in the right ventricular work index were studied. Of these patients 204 had clearly established congenital heart disease, 32 had mitral stenosis, and 9 had chronic cor pulmonale. The data for each clinical entity are presented separately and then analyzed on a composite basis. It was found that there was no single electrocardiographic lead which unfailingly (consistently) indicated right ventricular preponderance, but that through the analysis of $V_{3R}$ or $V_1$ plus $aV_R$ and VE the detection of right ventricular preponderance will be missed only rarely. The presence of a tall, predominant late R wave in lead $aV_R$, provided the heart was in a vertical cardiac position, was found to be a reliable index

of right ventricular preponderance in infants, children, and adults, whereas the adult electrocardiographic criteria for this condition, based on various R/S ratios in the right precordial leads, was misleading, particularly if applied to infants and children. In patients with congenital heart disease and presumed right ventricular hypertrophy, the most common electrocardiographic finding was that of a complicated incomplete right bundle branch block pattern consisting of (1) a predominant, late R wave in $aV_R$, (2) a QRS complex over the left precordial leads, (3) an R′ wave of 10 mm. or greater, and (4) a delay in activation of the R′ of the incomplete right bundle-branch block. Combined ventricular preponderance was suggested by the presence of incomplete right bundle-branch block in the right precordial leads, a delay in ventricular activation time of the left ventricular R wave, and a Q/R ratio approaching unity in $aV_R$.

SAGALL

**Fletcher, E., and Brennan, C. F.: Paroxysmal Auricular Tachycardia with Auriculo-Ventricular Block.** Brit. M. J. **2**: 792 (Oct. 5), 1957.

Paroxysmal atrial tachycardia with atrioventricular block is usually a complication of excess digitalis administration. Although the presence of this arrhythmia may be suspected, it cannot be differentiated clinically from atrial fibrillation. The electrocardiogram must be inspected closely to detect the presence of pathognomonic P waves separated by isoelectric intervals. Treatment includes stopping the digitalis and conserving, as well as replacing, body potassium. Four patients properly diagnosed and treated are described. Continued digitalis administration in the presence of this arrhythmia (when produced by prior digitalis) may be disastrous. The authors, however, point out that this arrhythmia may occur spontaneously. When this happens, the condition is apparently benign and paradoxically the use of digitalis is the treatment of choice.

KRAUSE

**Jolly, F., Carlotti, J., Servelle, M., Peroz, A., Colin, R., Forman, J., Laurens, P., Azerad, N., Lucchini, B.: Catheterization of Left Cardiac Cavities: (Comparative Study of Transbronchial and Transthoracic Methods of Approach.)** Arch. mal. coeur **50**: 782 (Sept.), 1957.

Left heart catheterization in 83 patients showed that the transbronchial method was faster and easier, and was not accompanied by pain during penetration of the pericardium or by stubborn pleural effusion, as was the transthoracic method in 2 patients. However, the transbronchial route was less comfortable for the patient and had the disadvantage that it was sometimes more difficult to puncture a small left atrium or to penetrate into the aorta, and that marked tachycardia resulted from the bronchial anesthesia. As the pulmonary capillary pulse was shown to be almost identical with the left atrial pulse (showing only a delay of about 0.1 second), the value of left heart catheterization in mitral disease was limited to determination of left ventricular filling pressure. It was more useful in the diagnosis of valvular and subvalvular aortic stenosis, especially if it was combined with mitral disease. At any rate it was not a routine method and should be used in selected cases only.

LEPESCHKIN

**Effert, S., Rippert, R., and Schaub, W.: Electrocardiogram and Phonocardiogram in Atrial Septal Defect.** Arch. Kreislaufforsch. **27**: 171, (Oct.), 1957.

Of 50 patients with atrial septal defect, confirmed by operation or cardiac catheterization, 41 showed incomplete and 6 complete right bundle-branch block. All 7 patients with a foramen primum type of defect showed marked left axis deviation of the greatest QRS vector (+3° to —164°), while in 37 of the 39 patients with a foramen secundum type this vector had an axis of +5° to +150°; 2 patients (one of them obese) had axes of —14° and —26°. The magnitude of this vector was much greater in the "primum" than in the "secundum" type, and the incidence of a "P congenitale" pattern was greater. A P-R interval exceeding 0.18 second was found in all "primum" cases, but in only 20 per cent of "secundum" cases; a P-R of 0.30 was found in 4 of the "primum" but none of the "secundum" cases. There was no correlation between the right ventricular pressure and the QRS duration or the angle between the QRS complex and the T wave. The pattern of right ventricular hypertrophy was seen in 2 patients, that of acute right ventricular strain in 1; these had a right ventricular pressure exceeding 55 mm. After operative treatment the QRS complex usually became narrower while the T wave became inverted in the precordial leads due to post-operative pericarditis. A systolic murmur with a pulmonic maximum was found in all of 47 phonocardiograms, a short protodiastolic murmur in 9, a presystolic murmur in 3, and a split second sound in 41.

LEPESCHKIN

**Rijlant, P.: Direct High Speed Cinematographic Registration of the Human Vectorcardiogram.** Acta Cardiol. **12**: 258 (Fasc. 3), 1957.

A method is described for high-speed cinematography of the human vectorcardiogram. Sev-

enty-two electrodes, distributed at regular intervals on the body surface, were connected to a tridimensional network with infinite resistance. The current flow within the system was such that measurements of potentials gave values equivalent to the actual generators within the heart and permitted construction of true vectorcardiograms in the conventional planes. The vectorcardiograms were developed on the screen of a memoscope of the Hughes' Aircraft Company. The memoscope was started when the speed of a high speed camera had attained a certain value. Comparison of successive frames gave valuable information concerning high frequency components of the vectorcardiogram, and permitted direct visualization of the chronological order of events in the vectorcardiogram and their accurate analysis.

PICK

**Wolff, L.: Vectorcardiographic Diagnosis of Coronary Artery Disease.** J.A.M.A. **165:** 1784 (Dec. 7), 1957.

The electrocardiographic diagnosis of posterior myocardial infarction may be difficult. Most important diagnostic clues are Q waves in lead II, III, and $aV_F$. Since Q waves can occur in these leads in normal individuals, significant Q waves are recognized by their size and duration. The unreliability of these criteria becomes apparent with but little experience. It is estimated that 60 to 70 per cent of the acute and 10 per cent of old lesions only can be recognized. To distinguish normal electrocardiograms from those with inferior myocardial infarction or pulmonary embolism is often difficult or impossible. However, with vectorcardiograms an inferior infarct is manifested by increased duration and magnitude of the initial superior QRS forces, clockwise inscription, and wide sweep of the loop in its frontal projection together with smallness or absence of terminal forces oriented to the right of or superiorly to the O point. Pulmonary embolism was manifested in a broad clockwise inscription of the QRS loop in its frontal projection with large rightward terminal forces and no slowness in inscription. Therefore, the vectorcardiogram is of great diagnostic value because it clarifies to a degree not attained with the electrocardiogram the differentiation between normal findings, posterior myocardial infarction, and pulmonary embolism.

KITCHELL

**Lindeneg, O., and Rasmussen, K. N.: The Prognosis in Bundle Branch Heart Block.** Acta med. scandinav. **158:** 453 (Oct. 15), 1957.

After a review of the literature concerni prognosis in bundle-branch block, the autho present their own study of 337 hospital patien with this abnormality diagnosed during the yea 1936 to 1950 with an observation period of 4 t 19 years. Prognosis was determined according t actuarial principles. They found the outlook t be less favorable in patients with left bundl branch block than with right bundle-branch bloc The prognosis was the same for both the classic type right bundle-branch block and the "Wilson type with the broad, low S wave in lead I or i leads I and II. The clinical condition and th underlying heart disease appeared to be the d ciding factors in prognosis. In patients wit coronary occlusion, congestive heart failure, an enlarged heart in addition to bundle-branch block the outlook was poor. The prognosis also wa less favorable for men than women and fo younger than older persons. Patients who sur vived the first year had a relatively good prog nosis. The prognosis also seemed to be worse fo hospitalized rather than ambulant patients.

BROTHERS

**Bilger, R., Sander, J., Reindell, H., and Klepzig, H.: Vectorcardiographic Findings in Overload of the Right Heart.** Arch. Kreislaufforsch. **27:** 117 (Oct.), 1957.

In 66 patients with right ventricular overload the horizontal vectorcardiogram (cube system) showed 4 types. Type I, showing normal initial vectors but terminal vectors directed to the right, with clockwise rotation of the loop, corresponded to the lowest values of right ventricular pressure. Type II showed a more anterior course of the terminal section, with the entire loop showing clockwise rotation. Type III, showing marked displacement of this section anteriorly and to the right, corresponded to the highest pressures. Type IV showed a narrow loop, deviated little anteriorly but considerably to the right; it was usually found in chronic cor pulmonale with no signs of right ventricular hypertrophy in the precordial leads. The mean QRS vector, determined by addition of instantaneous vectors at intervals of 1/400 second, showed a deviation anteriorly, downward and to the right, approximately parallel to the mean right ventricular pressure. The degree of terminal slowing of the vector loop showed no relation to this pressure. The T-wave vectors showed a tendency to deviate in a direction opposite to that of the mean QRS vector.

LEPESCHKIN

**Gross, D.: The Apex of Ventricular Extrasystoles—Its Diagnostic and Clinical Significance.** Ztschr. Kreislaufforsch. **46**: 905 (Dec.), 1957.

Ventricular extrasystoles with a sharp apex of the QRS complex in standard limb leads corresponded to an otherwise normal electrocardiogram in 83 per cent, normal heart size in 90 per cent, and a clinically normal heart in 73 per cent. In extrasystoles with a slurred apex these percentages were 57, 40 and 13 respectively, while in those with a notched apex they were practically zero. The duration of the QRS complex was practically the same in the 3 groups of extrasystoles, while the average amplitude of QRS was 19.1 mm. in the first, 10.4 mm. in the second, and 7.5 mm. in the third group. The amplitude of the QRS complex is accordingly more important than its duration in the differentiation between clinically significant and harmless extrasystoles.

LEPESCHKIN

**Jungmann, H., and Gadermann, E.: Pathologic Physiology of the Arterial Pulse in Various Circulatory Disturbances. IV. The So-called Preliminary Wave in the Peripheral Pulse.** Ztschr. Kreislaufforsch. **46**: 893 (Dec.), 1957.

In the femoral, and sometimes also in the crural pulse of most younger persons, a small wave precedes the steep ascent of the pulse by an interval of 0.08-0.15 second, independent of the heart rate. In old persons this wave is much less pronounced. In complete atrioventricular dissociation each P wave is followed by a similar wave in the femoral pulse, but the automatic ventricular beats do not show a preliminary wave; this wave could therefore not be attributed to the ventricular isometric phase of contraction. On the other hand, it appeared regularly in cases of atrial flutter and fibrillation, and therefore could not be attributed to atrial contraction. It is held more probable that it is caused by a change of tension in the arterial wall preceding the pulse wave.

LEPESCHKIN

**Burch, G. E.: Significance of Certain Early Changes in the T Wave in Coronary Disease.** A.M.A. **165**: 1781 (Dec. 7), 1957.

The electrocardiogram is a useful adjunct to clinical cardiology when integrated intelligently with all the clinical data. The able physician treats the patient and not his electrocardiogram. Close inspection of the S-T segment and T wave reveals many subtle changes. The earliest electrocardiographic change that develops with coronary disease is lowering of the S-T segment or early portions of the ascending limb of the T wave. As coronary disease advances, the changes in the T wave will indicate a progressively worse condition, and more and more of the initial portion of this wave becomes lower and isoelectric. Then the early portion of the T wave may become depressed below the isoelectric line even though the terminal portion remains positive. The T waves become lower, isoelectric, and then negative, and finally there occurs the ischemic T wave with coving. For most effective preventive and curative therapy, coronary disease should be detected at its inception. It is imperative, therefore, to identify the earliest and most subtle electrocardiographic changes that are produced by coronary disease. On the other hand, improper use or treatment of the electrocardiogram rather than the patient is untenable. The value of a properly recorded electrocardiogram is directly related to the wisdom of its interpretation.

KITCHELL

## ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

**Marshall, J. R., and Pantridge, J. F.: Pericardiectomy for Chronic Constrictive Pericarditis.** Lancet **2**: 1039 (Nov. 23), 1957.

Seventeen patients underwent pericardiectomy for chronic constrictive pericarditis. However, slow and incomplete recovery followed limited pericardiectomy. In later cases, a catheter was placed in the vena cava during operation. In 4 of 5 cases, the venous pressure did not fall significantly after ventricular clearing, but it fell abruptly when the atria were cleared and usually further when the great veins were decorticated. The desire to restore normal circulatory dynamics must be weighed against the risk of extensive decortication.

KURLAND

**Selye, H.: Humoral "Conditioning" for the Production of a Suppurative, Acute Myocarditis by the Oral Administration of Sodium Phosphate.** Am. Heart J. **55**: 1 (Jan.), 1958.

Experiments in rats are reported showing that orally administered monobasic sodium phosphate not only increases the cardiotoxic actions of vitamin D preparations, but qualitatively changes them so that an acute purulent myocarditis results. This effect was enormously enhanced by concurrent treatment with 2 ($\gamma$)-methyl-9 ($\gamma$)-chlorocortisol (Me-Cl-COL). Incidentally it was noted that the severe nephrocalcinosis normally produced by combined treatment with dihydrotachysterol (DAT) and monobasic sodium phosphate ($NaH_2PO_4$) is also further aggravated by concurrent treatment with Me-Cl-COL.

SAGALL

**Plum, G. E., Bruwer, A. J., and Clagett, O. T.: Chronic Constrictive Pericarditis. Roentgenologic Findings in 35 Surgically Proved Cases.** Proc. Staff Meet. Mayo Clin. **32**: 555 (Oct. 2), 1957.

The authors describe the x-ray findings as they occurred in 35 surgically proved patients with chronic constrictive pericarditis. When there is clinical evidence of congestive heart failure, certain x-ray manifestations strongly suggest chronic constrictive pericarditis rather than exclusively intrinsic myocardial disease. Forty-nine per cent of the patients had pericardial calcification by roentgenogram. The commonest site of calcification was high on the left border of the heart in the region where opposite pulsations are observed fluoroscopically. The second commonest site of calcification was along the sternal and diaphragmatic surfaces of the right ventricle, and this was best seen in lateral or oblique projections. The third commonest site was in the coronary sulcus between the left atrium and left ventricle. Fourteen patients had changes in their cardiac contour. These changes obliterated the "waist" of the heart, which usually assumed a globular shape. Cardiac fluoroscopy is a very important aid in the diagnosis of chronic constrictive pericarditis. It was of positive value in 77 per cent of the 26 patients in whom it was utilized. Decreased or absent pulsations along the cardiac borders are most important, particularly when the heart is small or of normal size. Localized limitation of pulsation is particularly in favor of constrictive pericarditis rather than diffuse myocardial disease. A large left atrium may be seen in chronic constrictive pericarditis, but when this is so, pulmonary vascular constriction is less marked than it is in myocardial stenosis. The large left atrium is usually ascribed to constriction of the left ventricle or the atrioventricular groove. Also, septal lines due to engorged pulmonary lymphatics are rare in chronic constrictive pericarditis and are said to be common in mitral stenosis. It is well to remember that none of the roentgen findings are in themselves diagnostic of chronic constrictive pericarditis without the usual clinical findings.

KRAUSE

## HYPERTENSION

**Wilson, C., Ledingham, J. M., and Cohen, M.: Hypertension Following X-irradiation of the Kidneys.** Lancet **1**: 9 (Jan. 4), 1958.

Two patients are described who received deep x-ray therapy for malignant disease and subsequently developed hypertensive renal disease. The contrasting histologic patterns suggested the dual nature of irradiation damage to the kidneys in man. In 1 were noted features characteristic of irradiation nephrosclerosis such as diffuse interstitial fibrosis and fibrohyaline glomeruli; in the other, acute arterial and glomerular necroses were the most prominent lesions, suggestive of malignant essential hypertension. Following irradiation of the exteriorized kidneys in the rat, hypertension developed after a latent period and the histologic picture of irradition sclerosis was produced. Where 1 kidney was exteriorized and irradiated, the irradiated kidney was grossly contracted, but the extent and severity of the lesion of the nonirradiated kidney were related to the degree and duration of the hypertension. Irradiation of both kidneys in situ produced hypertension not accompanied by irradiation sclerosis. Thus, the observations in man and the experiments in rats show that x-irradiation of the kidneys may produce 2 biological effects—interstitial fibrosis and hypertension. These appear to be independent of one another.

KURLAND

**Janku, I., Raskova, H., Motl, O., and Blazek, Z.: On the Hypotensive Effect of an Extract of Olives.** Arch. int. pharmacodyn. **112**: 342 (Nov. 1), 1957.

The effect of a water extract of leaves of olive (*Olea europea* L.) on blood pressure was studied. The effect on blood pressure was tested in the cat and dog; its influence on vagal stimulation and on the effect of acetylcholine was also studied. The action of the extract was compared to the effect of choline. Small doses (0.1 to 0.4 mg.. per Kg.) of the extract had a transitory hypotensive effect; this was of longer duration in the dog than in the cat and was suppressed by atropine. Larger doses produced multiphasic variations of blood pressure; this action was not influenced by atropine. The extract did not modify the effect of vagal stimulation or of acetylcholine on the blood pressure; it increased the effect of epinephrine and of preganglionic sympathetic stimulation. Its action was similar to the effect of choline; it differed, however, in having a greater nicotinic than muscarinic effect.

CALABRESI

**Allanby, K. D., and Trounce, J. R.: Excretion of Mecamylamine after Intravenous and Oral Administration.** Brit. M. J. **2**: 1219 (Nov. 23), 1957.

Hypertensive patients without renal involvement were studied. This was done to assess the absorption of mecamylamine from the alimentary tract. When this drug is administered orally, 55 to 75 per cent of it may be recovered from the urine, which seems to indicate adequate absorp-

tion. Also, excretion is steady and prolonged with a smooth and sustained fall of blood pressure following a single oral dose. Hence, blood pressure control should be easily obtained with infrequent oral dosage and blood pressure level should not fluctuate as much as it does with other ganglionic-blocking agents. If the urine is alkalized or if acetazolamide is administered concurrently with mecamylamine, the excretion of mecamylamine is almost entirely prevented. This may cause accumulation of the drug and a prolonged fall of blood pressure will result.

KRAUSE

**Spühler, O., and Scheu, H.: Analytic Investigations of Effects of Serpasil and Ecolid on Blood Circulation in Arterial Hypertension.** Cardiologia **31**: 51 (Fasc. 1), 1957.

The authors applied the pulse-pressure method of Wezler and Brömser-Ranke to determine acute circulatory alterations effected by antihypertensive agents. This method has advantages over other technics in permitting continuous observations of acute short-lasting changes in hemodynamics. Thus, in acute experiments, Serpasil and Ecolid, applied for short periods of time caused a reduction of cardiac output and an increase in the peripheral resistance, while with extended treatment adaptation took place. In the opinion of the authors increase in peripheral resistance cannot be explained by arterial vasoconstriction consequent to a fall in blood pressure. They imply a mechanism of venostasis causing elevation of venous and thus total resistance, which in turn causes reduction of stroke volume and cardiac output due to diminished venous return.

PICK

## METABOLIC EFFECTS ON CIRCULATION

**Davis, O., Goodkind, M. J., Pechet, M. M., and Ball, C., Jr.: Increased Excretion of Aldosterone in Urine from Dogs with Right-Sided Congestive Heart Failure and from Dogs with Thoracic Inferior Vena Cava Constriction.** Am. J. Physiol. **187**: 45 (Oct.), 1956.

Extracts of urine from 11 normal dogs, 9 dogs with cardiac failure and 10 dogs with thoracic inferior vena cava constriction and ascites were assayed for aldosterone-like activity. The activity in urine from dogs with heart failure and from dogs with thoracic caval constriction was equivalent to 52 and 167 $\mu$g. per day of desoxycorticosterone acetate (DCA), respectively and renal sodium excretion was uniformly low. No activity was detected in 4 days' urine from normal dogs but chromatographic fractionation and assay of a 26-day collection of normal dog urine showed sodium-retaining and increased potassium-excreting activity in the aldosterone fraction only. Following bilateral adrenalectomy and discontinuation of DCA therapy in 2 dogs with caval constriction, all urinary aldosterone-like activity disappeared and a natriuresis occurred. Assays of chromatographic fractions of extracts of urine from dogs with heart failure and from dogs with caval constriction revealed activity only in the aldosterone fraction.

OPPENHEIMER

**Grauer, H.: The Adrenosinetriphosphoric Acid Content of Myocardium in Normal, Anoxemic and Hypocalcemic Conditions.** Cardiologia **31**: 86 (Fasc. 1), 1957.

In adult healthy rats acute oxygen deficiency causes a fall in the adenosinetriphosphate (ATP) content of the ventricles, starting with exhaustion of the glycogen reserves and continuing steadily to a minimum. This is associated with the development of bradycardia terminated by cardiac arrest. In the electrocardiogram one sees progressive shortening of the QT duration. All these observations are in keeping with St. Györgyi's theory of muscular contraction. If these experiments are performed after induction of severe hypocalcemia by sodium fluoride or oxalate, the ATP concentration in the myocardium remains almost normal, even up to cardiac standstill, and the QT interval lengthens progressively. This can be explained on the basis of Fleckenstein's theory of contraction by assuming a severe disorder of membrane permeability in hypocalcemic muscle fibers. The significance of the 2 theories for the understanding of contraction under various conditions is briefly discussed.

PICK

**Beuren, A., Sparks, C., and Bing, R. J.: Metabolic Studies on the Arrested and Fibrillating Perfused Heart.** Am. J. Cardiol. **1**: 103 (Jan.), 1958.

Myocardial metabolism was studied in 40 dogs by means of an open or a closed technic. In the open chest animal, myocardial oxygen usage was significantly less in the fibrillating than in the regularly contracting heart, and in the potassium-arrested heart it was slightly lower yet. Myocardial balances of glucose, lactate, ketones, and pyruvate were mostly negative during the control period, probably due to technical difficulties. The closed technic, which appeared to be physiologically more valid, disclosed no significant difference in oxygen usage by the regularly contracting empty heart as compared with the fibrillating or

arrested one. Myocardial extraction of glucose, lactate, and ketones occurred in the regularly contracting heart, but these balances became negative during cardiac arrest or fibrillation. It is suggested that cardiac oxygen usage is primarily determined by its external work, and that previous values calculated for the mechanical efficiency of the beating heart are too low.

ROGERS

## PHARMACOLOGY

**Ditlefsen, E.M.L.: Quinidine Concentration in Blood and Excretion in Urine Following Parenteral Administration as Related to Congestive Heart Failure.** Acta med. scandinav. **159:** 105 (Nov. 15), 1957.

This study was designed to determine whether or not patients with congestive heart failure obtain a higher blood level of quinidine and excrete less of the drug in the urine than do patients without congestive heart failure. Ten normal individuals in good health and 9 cardiac patients in congestive heart failure with enlarged livers were given single intramuscular injections of 0.84 Gm. of quinidine chloride. In all tests done from 2 to 12 hours after the injection, patients with congestive heart failure obtained considerably higher concentrations of quinidine in the blood than did the control group. After 12 hours, the difference was at its greatest with the congestive heart failure group having a quinidine blood level more than double that of the control group. The excretion of quinidine in the urine was much lower with the cardiac patients than with the control group in the first 12 hours. During the next 12 hours the quinidine excretion by the cardiacs was slightly greater than with the control group. The average urinary quinidine excretion for the 24-hour period was, however, greater in the control subjects than in the patients with heart disease. The author is of the opinion that the increased blood levels of quinidine seen in the patients with congestive heart failure is due to delayed urinary excretion of quinidine and to liver damage that interferes with the liver's role in the metabolism of quinidine. He believes that in the presence of chronic congestive heart failure with hepatic enlargement, a greater degree of caution must be exercised in the use of quinidine because of the greater risk of intoxication in these patients.

BROTHERS

**Cotton, M. V., Moran, N. C., and Stopp, P. E.: A Comparison of the Effectiveness of Adrenergic Blocking Drugs in Inhibiting the Cardiac Actions of Sympathomimetic Amines.** J. Pharmacol. & Exper. Therap. **121:** 183 (Oct.), 1957.

This report describes the effectiveness of adrenergic blocking drugs in inhibiting the increase in cardiac contractile force elicited by levarterenol. epinephrine and isoproterenol in the dog. The 5 drugs used were phentolamine HCL (Regitine), phenoxybenzamine HCL (Dibenzyline), piperoxan HCL (Benodaine) azapetine phosphate (Ilidar), and dihydrogenated ergot alkaloids (Hydergine). The force of cardiac contraction was measured with a strain-gage arch sutured to the right ventricle. Each blocking drug was studied both in dogs anesthetized with barbiturates and in dogs anesthetized with morphine-chlorolose. Phentolamine and Dibenzyline completely blocked the cardiac actions of the amines, whereas large doses of piperoxan and azapetine blocked the effects by 50 to 75 per cent. Hydergine, even in very large doses, produced only 15 to 30 per cent blockade. None of the blocking drugs had any demonstrable influence upon the increase in contractile force produced by ouabain.

RINZLER

**Kessler, R. H., Lozano, R., and Pitts, R. F.: A Comparison of the Pharmacological Behavior of Chlormerodrin, Meralluride, Mersalyl and Mercuric Chloride in the Dog.** J. Pharmacol. & Exper. Therap. **121:** 432 (Dec.), 1957.

This investigation compared the behavior in the dog of inorganic mercuric ion (mercuric chloride) and 3 organic mercurial diuretics (mersalyl, meralluride, and chlormerodrin) when given intravenously in doses containing equivalent amounts of mercury at 3 dose levels (1.0, 2.0, and 4.0 mg. per Kg. of mercury). The data collected included disappearance of the materials from the blood plasma, distribution in tissues, uptake by the kidneys, urinary excretion of the administered mercury, glomerular filtration rate, and renal tubular reabsorption of sodium and urine flow. The 4 compounds induced diuresis by partially blocking the renal tubular reabsorption of salt and water, so that quantitative rather than qualitative differences distinguished the 4 agents. Blockade of reabsorption and onset of diuresis developed more slowly after mercuric chloride than after the others and the urinary excretion of inorganic mercury was slower. Mercuric chloride depressed glomerular filtration rate more than did the organic mercurials, especially at high dose levels. All 4 agents were rapidly removed from the blood stream and became concentrated in kidney cortex. This concentration did not correlate well with diuretic activity.

RINZLER

**Sprager, M. W.: Digitalis Intoxication. A Review and Report of Forty Cases, with Emphasis on Etiology.** Arch. Int. Med. **100:** 881 (Dec.), 1957.

The premise of this paper is that it is possible to titrate closely the required amount of digitalis for each patient in congestive heart failure. If this is true, under-digitalization and digitalis intoxication should rarely occur. Rigid standards to diagnose digitalis intoxication were applied in 40 selected patients with an average age of 65 years. Apparently neither the severity of the disease nor the type of myocardial disease was important in the production of toxicity. Symptoms usually preceded the signs of toxicity, but in general digitoxin produced more severe toxicity with less marked symptoms than did digoxin. In general, it was documented that digitalis toxicity could increase the signs and symptoms of heart failure. Anorexia, nausea, and vomiting are the best clues to overdigitalization. Arrhythmias occurred in 95 per cent of the cases and of these the most common was ventricular premature beats often leading to bigeminy. An attempt was made to clarify etiology based on correctable human error in the use of the drug. In this respect 80 per cent of the reported cases were preventable by the physician and 80 per cent of these were attributed to errors in drug dosage. In 23 per cent of the patients, the error was due to the use of augmented digitalis dosage in an adequately digitalized patient in intractable heart failure. A relatively common error was the failure to recognize the need for individualization of digitalis dosage or for periodic re-evaluation of dosage requirement coincident with alterations in the clinical state of the patient. In 10 per cent of the patients electrolyte imbalance was primarily indicted for the occurrence of toxicity. Two patients with toxicity due to the use of intravenous calcium were reported and 1 of these proved fatal. Re-emphasis is placed on stopping digitalis and using potassium in the face of digitalis toxicity. The average time for the disappearance of the signs and symptoms of digitalis toxicity was 2 to 3 days with digoxin and 9 to 11 days with digitoxin in the patients studied.

KRAUSE

**Raab, W., and Gigee, W.: Influence of Nicotine and Hexamethonium on the Catecholamine Content of the Dog's Heart.** Arch. int. pharmacodyn. **112:** 297 (Nov. 1), 1957.

The influence of nicotine on the catecholamine content of the dog's heart was tested to investigate the mechanism of action of this drug on the cardiac autonomic system. The interference of hexamethonium on the effects of nicotine was also studied. The content in total catecholamines, as defined in previous articles, was measured by a colorimetric method; the content of norepinephrine and epinephrine was determined by the bioassay method of von Euler. Short infusions of nicotine produced, after a very transitory bradycardia, a marked cardiac acceleration, lasting 1 to 2 minutes. Longer infusions caused bradycardia and arrhythmia; they also had a negative inotropic effect; 9 out of 10 dogs receiving 1 mg. per Kg. per minute of nicotine died during the infusion, within 5 to 10 minutes. While hexamethonium had no appreciable direct effect on the cardiac rate, it prevented, however, these effects of nicotine. The short infusion did not alter the total catecholamine content of the heart or its fractions. The prolonged infusion produced an increase in norepinephrine without an increase in the total catecholamine content. This was interpreted as due to stimulation of the sympathetic cardiac ganglia and also to increased secretion by the adrenal glands. After combined hexamethonium and nicotine administration the total catecholamine content was decreased, probably due to the sympathetic blocking of hexamethonium; bioassay determination of norepinephrine was not feasible, because it was impossible to separate the hexamethonium from the cardiac extract.

CALABRESI

**Scherf, D., Reid, E. C., and Chamsai, D. G.: Strophanthin Therapy in Atrial Flutter.** Am. J. M. Sc. **234:** 180 (Aug.), 1957.

The response of 18 patients with atrial flutter to the administration of strophanthin was studied during 22 attacks of arrhythmia. The initial dose of the drug was 0.125 mg. given intravenously after which serial electrocardiograms were obtained. If no effect was observed and extrasystoles were not produced, the dose was increased to 0.25 mg. daily. In some instances, 0.5 mg. was given daily. Conversion of atrial flutter to atrial fibrillation occurred in 8 attacks and to normal sinus rhythm in 6 others. Six patients did not respond to therapy and 4 of these died within a few weeks of their underlying noncardiac disease. One patient showed an increase in atrioventricular block from 2:1 to 4:1. There was 1 instance of nausea and vomiting; in none was ectopic rhythm produced. The results demonstrate that the incidence of conversion of atrial flutter into sinus rhythm or atrial fibrillation with strophanthin compares favorably with the results of digitalis therapy.

SHERMAN

**de Vleeschhouver, G. R., King, T. O., Poulsen, E., and Rovati, A. L.: Action of Chlorpromazine on the Vagal Cardio-Inhibitory Center.** Arch. int. pharmacodyn. **112**: 485 (Nov.), 1957.

To investigate the effects of chlorpromazine on the excitability of the vagal cardio-inhibitory center, the technic of the isolated, perfused head, connected to its trunk by means of the vagi nerves only, was used in dogs. Direct excitation of the vagal cardio-inhibitory center was induced by acute anoxia. Carotid sinus stimulation was induced by producing hypertension in the perfused head, through injection of epinephrine in the donor's circulation. Reflex cardiac slowing was elicited by electric stimulation of the carotid sinus nerves. Repeated injection of chlorpromazine into a common carotid artery of the isolated head did not modify the effect of these stimuli on the vagal cardio-inhibitory center.

CALABRESI

**Dasgupta, S. R.: The Effect of Chlorpromazine on Antidiuresis Produced by 5-Hydroxytryptamine (Serotonin) in Rats.** Arch. int. pharmacodyn. **112**: 264 (Nov. 1), 1957.

The effect of chlorpromazine (5 mg. per Kg. by intraperitoneal injection) on water diuresis was studied in male white rats, before and after the subcutaneous injection of serotonin (40 mg. per 100 Gm.). While chlorpromazine does not have a significant influence on diuresis of hydrated rats, it counteracts the marked antidiuretic effect of serotonin. In parallel experiments it was shown that chlorpromazine did not affect the antidiuretic effect of the posterior pituitary hormone. The mechanism of serotonin inhibition on water diuresis, whether secondary to preferential constriction of the afferent glomerular arterioles or to specific tubular increased water reabsorption, was not elucidated by these investigations. It was pointed out that, in the dog, it had been found that serotonin had the highest concentration in the hypothalamus and in other areas of the brain, which showed also a marked depressant effect from chlorpromazine.

CALABRESI

**Pines, I.: The Influence of Intravenously or Intracardially Administered Acetazole Amide upon Cardiac Function of Dogs.** Arch. int. pharmacodyn. **112**: 84 (Oct.), 1957.

The evidence of direct cardiac pharmacologic effects of the sulfonamides is summarized. These data and observations of beneficial effects of acetazole amide in cardiac patients, independent of its diuretic action stimulated the present study. In 14 open-chest dogs prepared with nembutal anesthesia and artificial respiration, the intra-atrial electrocardiograms and the arterial blood pressure were recorded. Intravenous injection of acetazole amide, in amounts of 100 to 1000 mg., caused a slight fall in arterial pressure, electrocardiographic changes (inversion of the T wave, changes in amplitude of the QRS complex, prolonged P-R interval), and bradycardia. Injection in the right atrium was frequently followed by transitory atrial fibrillation; this was probably not merely a mechanical effect of the injection itself, because a preliminary injection of tubocurarine prevented the arrhythmia. Similar effects were noted with right intraventricular injection of the drug. Acetazole amide potentiated the effects of intravenous or intracardiac injection of acetylcholine, digitoxin, or reserpine. Although it is possible that these effects result from cholinesterase inhibition, the mechanism of action is not elucidated by the present study.

CALABRESI

**Bryant, M. F., and Howard, J. M.: Necrotizing Properties of Metaraminol (Aramine) and Arterenol (Norepinephrine). Comparative Study.** Arch. Surg. **75**: 1020 (Dec.), 1957.

Two vasopressor drugs, metaraminol (Aramine) and levarterenol (Levophed; l-norepinephrine) currently used in the treatment of various acute hypotensive states were tested to determine their ability to produce local toxic manifestations in soft tissues. The experiments were performed on dogs. An intravenous infusion of either drug for a period of 3 hours resulted in spasm of the vein receiving the infusion but no soft tissue slough. Rapid subcutaneous injections of the drugs—even in concentrated solutions—did not produce tissue necrosis but yielded blanching and swelling, which gradually improved. A slow drip infusion of levarterenol given subcutaneously, routinely resulted in the formation of a large soft-tissue slough. Sloughing of tissue did not occur when a comparable dose of metaraminol was given in a similar fashion. It would seem, from these experiments, that metaraminol can apparently be given by intravenous drip infusion without the danger that inadvertent extravasation will lead to extensive soft-tissue sloughs.

BROTHERS

## PHYSICAL SIGNS

**Neill, C., and Mounsey, P.: Auscultation in Patent Ductus Arteriosus: with a Description of Two Fistulae Simulating Patent Ductus.** Brit. Heart J. **20**: 61 (Jan.), 1958.

The authors describe the auscultatory and phonocardiographic features in 73 patients with

patent ductus arteriosus. In all but 4 who had pulmonary hypertension, a loud continuous murmur was frequently accompanied by a thrill audible in the pulmonary area. Phonocardiography revealed the murmur to occupy the entire cardiac cycle or all but a short gap before and after the first sound. The murmur was accentuated at the second sound. In 34, multiple clanging eddy sounds, variable from beat to beat, were found. These frequently obscured the second sounds. These sounds and the murmur disappeared after closure of the ductus except for an occasional insignificant systolic murmur. In 8 of 22 patients with a large shunt, a middiastolic apical murmur was audible and in 5 an opening snap, both of which disappeared after closure. In the 4 with pulmonary hypertension, the continuous murmur was replaced by a soft systolic murmur and 3 had the diastolic murmur of pulmonary regurgitation. Two of these had a reversed shunt and an additional right atrial systolic murmur. The murmur of an arteriovenous aneurysm had a similar accentuation at the second sound but developed its crescendo later. One patient with a coronary right ventricular fistula and another suspected of having aorto-pulmonary septal defect had murmurs indistinguishable from those of a patent ductus arteriosus.

SOLOFF

## SURGERY AND CARDIOVASCULAR DISEASE

**Schimert, J. and Cowley, R. A.: Defibrillation, Cardiac Arrest, and Resuscitation in Deep Hypothermia by Electrolyte Solutions.** Surgery 41: 211 (Feb.), 1957.

This paper reports experiences with 47 dogs whose body temperatures were reduced to within a range of 15 to 29 C. and who were then deliberately fibrillated by electric stimulation. Normal cardiac rhythm was then restored with the use of electrolyte solutions combined with cardiac massage. Defibrillation was accomplished by injecting 2 to 3 ml. of a 15 per cent solution of potassium chloride directly into the left ventricle and forcing it into the coronary circulation by cardiac massage. The average time for successful defibrillation was 10 seconds. Transient cardiac standstill after potassium chloride was followed by spontaneous return to normal rhythm in 5 dogs.

After ventricular fibrillation was stopped, electrical activity in the myocardium was re-established by the injection into the left ventriele of 2 to 3 ml. of 10 per cent sodium lactate. Usually myocardial electric activity returned within seconds. Effective cardiac contractions were established by the injection into the left ventricle of 2 to 3 ml. of Ringer's lactate (25 times concentrated). Cardiac massage was continued until the contractions became regular and sustained. A slow intravenous infusion of 10 ml. of 10 per cent gluconate in 200 ml. of 5 per cent dextrose in water was used for cardiac dilatation and sluggish, feeble contractions.

Encouraged by the results of their efforts at controlling ventricular fibrillation and with an effective method for resuscitating the heart, the authors decided to use hypothermia and elective cardiac arrest by potassium chloride for intracardiac surgery. Seven dogs were subjected to left atriotomy or ventriculotomy at temperature ranging from 21 to 25 C. with exposure of the mitral valve for 5 to 8 minutes. The average time for cardiac arrest was 10 minutes. Cardiac resuscitation was accomplished with the use of sodium lactate, Ringer's lactate and cardiac massage. All animals survived the procedure. The authors hope that this technic may provide an opportunity for intracardiac surgery in the motionless human heart.

BROTHERS

**Bolton, H., Lazarides, D., Goldberg, H., and Downing, D. F.: Atrial Septal Defect. Experiences with One Hundred Cases Treated Surgically.** Arch. Surg. 74: 351 (March), 1957.

The results of attempts at surgical closure in 100 consecutive cases of atrial septal defect by atrioseptopexy, (an external suture technic guided by a finger inserted into the heart via the right atrial appendage) are reviewed. There is also a discussion of the anatomy, pathological physiology, and diagnosis of this disorder. The cases were separated into "ostium primum" or "ostium secundum" defects. Attempts at correction of the former were associated with a high mortality. Only 5 of 17 patients survived. Deaths were related chiefly to injury of the common atrioventricular conduction bundle and to postoperative circulatory failure. Of the 83 patients with ostium secundum defects, 13 died after surgery. Nine of the 3 had so called "blanced shunts"—that is, less than 1.5 liters left-to-right shunt with a calculable right-to-left shunt, however small. Eight of these 9 died. If, as the authors are presently doing, patients with balanced shunts are excluded from surgery, the mortality in septum secundum defects would have been 5.4 per cent. In 9 patients there was an associated mitral stenosis and 16 had anomalous drainage of the right pulmonary veins into the right atrium or venae cavae. The co-existence of these defects did not increase the risk provided they were also corrected. Preoperatively, some degree of pulmonary

hypertension was present in 64 per cent of this group of 83 patients and in 12 of the 13 patients who died. There was only 1 death from pulmonary embolism. The survivors were usually greatly benefited as evidenced by physiologic studies after surgery and symptomatic improvement. The authors believe atrioseptopexy to be the simplest, safest, and clinically the most satisfactory method of treatment for atrial septal defects available at this time provided that patients with defects of the ostium primum type and those with "balanced shunts" are excluded.

BROTHERS

**Mondini, P., Zaccarini, C., Cavalloni, Ziliotto, P., and Porro, A.: Pharmacological Arrest of the Heart for Cardiac Surgery.** Presse med. **65**: 103 (Jan. 19), 1957.

An experimental method is described for production of temporary arrest by pharmacologic means. The experiments were performed on Langendorff preparations of dogs' hearts and consisted of the injection of a mixture of novocaine, acetylcholine, and adenosine triphosphate. Of several injection sites tested, coronary perfusion proved most efficient. Cardiac arrest occurred in diastole, was always reversible with spontaneous resumption of the heart beat as soon as the perfusion was stopped. In no instance did the technic used lead to ventricular fibrillation. The authors visualize the possibility of application of this method to aid surgical procedures in the human heart.

PICK

**Read, R. C., DeWall, R. A., Warden, H. E., Ziegler, N. R., and Lillehei, C. W.: The Application of Arterialized Venous Blood to Intracardiac Surgery.** Surg., Gynec. & Obst. **104**: 457 (Apr.), 1957.

Two hundred and twenty-five pints of antecubital venous blood were collected after warming the hand and forearm in water at 46 C. for 10 minutes. This procedure increased the blood's oxygen content from an average of 70 per cent to 83 per cent saturation, slightly reduced the carbon dioxide content, and increased the pH. Breathing 100 per cent oxygen during venesection further increased the oxygen saturation to an average of 88.5 per cent making it more suitable for use in priming oxygenator systems employed in intracardiac surgery.

ROGERS

## VALVULAR HEART DISEASE

**Goodyer, A. V. N., and Glenn, W. W. L.: Management of the Circulatory, Inflammatory and Metabolic Complications of Mitral Valvulotomy.** New England J. Med. **257**: 735 (Oct. 17), 1957.

The authors present and discuss the origin and management of some of the complications of mitral valvulotomy. These include the sequelae of acute circulatory failure, prolonged hypotension postoperatively, acute congestive heart failure, rapid ventricular response to atrial arrhythmias, and persistent cardiac failure despite an apparently adequate valvulotomy; the inflammatory sequelae of bacterial endocarditis and the syndrome of pleuropericarditis after cardiotomy; and the metabolic complication of hyponatremia.

SAGALL

**Vela, J. E., Mata, L. A., and Torpey, A.: Rheumatic Mitral Valvulopathy with Interauricular Septal Defect. Study of 12 Cases, 8 with Autopsy and 4 Clinical.** Arch. Inst. Cardiol. **27**: 411 (July-Aug.), 1957.

In reporting 12 patients with Lutembacher's syndrome, the authors stress the rarity of this association of a very common disease and a relatively common malformation. Multiple valvular lesions have been found in each of these patients, in contrast with the observations reported by others. In most of these patients the diagnosis has been of rheumatic disease, usually with mitral and tricuspid valvular involvement; the co-existence of the interatrial septal defect was suggested by the lack of the presystolic crescendo, by the loud systolic pulmonary murmur, by the dilatation and pulsation of the pulmonary arteries, and by the right bundle-branch block. It is pointed out that the septal defect increases the flow of blood and therefore cannot much decrease the pressure in the pulmonary circulation; a co-existent tricuspid incompetence may however decrease the pulmonary congestion. The cyanosis is due to reversal of flow through the interatrial shunt, secondary to pulmonary hypertension. The radiologic signs of pulmonary hypertension and of right atrial enlargement with relatively little left atrial enlargement are stressed. Predominant right atrial enlargement is found also at autopsy. Although typically the Lutembacher syndrome should include only cases of defect of the septum primum, in some instances marked left atrial dilatation may produce incompetence of the valve of the foramen ovale. Arteriosclerotic changes of the pulmonary arterioles have not been found. The rheumatic etiology has been substantiated in the autopsy cases and is accepted also for the clinical observations.

CALABRESI

**Connolly, D. C., and Wood, E. H.: Hemodynamic Data during Rest and Exercise in Patients with Mitral Valve Disease in Relation to the Differentiation of Stenosis and Insufficiency**

**from the Pulmonary Artery Wedge Pressure Pulse.** J. Lab. & Clin. Med. **49:** 526 (Apr.), 1957.

Hemodynamic data obtained at cardiac catheterization during rest and exercise have been studied in 24 patients with mitral stenosis, 20 patients with mitral insufficiency, 3 patients with left ventricular failure in the absence of mitral valve disease, and 16 healthy subjects. When the pulmonary artery wedge mean pressure exceeded 20 mm. Hg, the peak V-wave pressure was significantly greater in mitral insufficiency than in mitral stenosis at equivalent levels of pulmonary artery wedge pressure, and there was no overlap between the 2 groups. This differentiation was thought to be of diagnostic significance. When pulmonary artery wedge mean pressures were less than 20 mm. Hg, no such distinction was found between patients with mitral stenosis, patients with mitral insufficiency, and healthy subjects. No systematically significant difference was found between the time of onset of the V-wave in relation to the Q-T intervals in the groups of patients with stenosis and insufficiency. The time of onset was relatively later in normal subjects. Pulmonary artery diastolic pressures were not systematically different from pulmonary artery wedge mean pressures when the wedge mean pressures were below 20 mm. Hg, but exceeded pulmonary artery wedge mean pressures when the latter were above 20 mm. Hg.

MAXWELL

**Korner, P., and Shillingford, J.: Tricuspid Incompetence and Right Ventricular Output in Congestive Heart Failure.** Brit. Heart J. **19:** 1 (Jan.), 1957.

The dye-dilution-curve method developed by the authors was used to estimate the degree of tricuspid valvular regurgitation in 14 patients with congestive failure and to correlate this estimate with the clinical findings and the necropsy findings in 6. This method depends upon the fact that for a given cardiac output and volume added valvular incompetence shortens the appearance time, decreases the maximum concentration, and prolongs the rate of fall of the descending limb of the curve. The actual regurgitant flow was computed from the change in the slope of the curve. Regurgitant flow from the right ventricle varied from 1.2 to 8.2 L. per minute and forward flow from 5 to 2.1 L. The total flow varied from 5 to 10 L. a minute. Exercise increased the regurgitant flow and, on occasion, decreased forward flow. Venous pressure did not correlate with regurgitant flow. Systolic pulsation of the liver required at least 3.5 L. per minute of regurgitant flow. Regurgitation was verified at necropsy by perfusion experiments. The ratio of regurgitant to forward flow depended upon the difference in pressures between the right atrium and pulmonary artery and also the difference in size of the tricuspid and pulmonary orifices.

SOLOFF

**Glenn, W. W. L., and McNeill, T. M.: Aortic Embolism Complicating Mitral Stenosis: With Particular Reference to Emergency Valvulotomy before Embolectomy.** New England J. Med. **256:** 295 (Feb. 14), 1957.

The authors advocate emergency mitral valvulotomy in patients with rheumatic heart with severe congestive heart failure and embolism to the aortic bifurcation prior to aortic embolectomy. A detailed report of a patient in whom this sequence was followed is reported. The patient, a woman aged 47 years, was moribund at the time of admission to the hospital and when the valvulotomy was done, 6 hours after the embolization. The authors give the following reasons for recommending the performance of the surgical procedures in the sequence indicated: (1) An adequate valvulotomy can be expected to reduce the hypertension in the right ventricle, pulmonary artery and left atrium with immediate partial relief of congestive heart failure; (2) the state of shock attending aortic embolism may be expected to be further aggravated by congestive heart failure; (3) the heart is in a better state after a valvulotomy to handle the increased venous return attendant upon a successful embolectomy; (4) additional emboli dislodged during the valvulotomy may be trapped above the aortic obstruction already present and be removed at the subsequent embolectomy; and (5) the outlook for functional recovery of the involved pelvic structures and lower extremities is greater in the presence of an increased cardiac output following a satisfactory valvulotomy.

ROSENBAUM

**Muller, C.: Aortic Stenosis and the So-Called Rheumatic Valvular Diseases in a Postmortem Material.** Acta med. Scandinav. **156:** 241 (Dec. 31), 1956.

The results of 8,663 postmortem examinations at the Oslo Municipal Hospital were reviewed and of this series a group of 509 patients with rheumatic valvular disease was found. Two 5-year periods, 1923 to 1927 and 1943 to 1947, were compared. The frequency and localization of valvular disease was identical in the 2 groups. Aortic valvular disease and mitral valvular involvement occurred with equal frequency (60 per cent) and isolated aortic stenosis occurred more frequently (34.8 per cent) than isolated mitral stenosis (30.5 per cent). Women predominated

in all subdivisions of localization except isolated aortic disease where men were in the majority. The average age at death was 61.5 years in the early group and 67.5 years in the group examined in 1943 to 1947. The average age at death was 7 to 10 years greater in women than in men, and the highest average age at death in patients with isolated aortic stenosis was 71.6 years. Of the patients with aortic stenosis, 87 per cent of those in whom it was an isolated lesion and 77 per cent of those in whom it was combined with other valvular disease reached the age of 60 years or more. This is about 10 years or more greater than that reported in comparable American studies. Calcification of the valves was present in 78 per cent of all valvular lesions and in 90 per cent of the patients with isolated aortic stenosis. Coronary sclerosis occurred in nearly three fourths of the patients with aortic stenosis and only 14 of the 106 patients showing this valvular lesion were spared atheromatous changes in the ascending aorta. Myocardial infarction was present in 12.3 per cent of the patients and was more common in association with aortic valvular disease. The author believes that the problem regarding the etiology of isolated aortic stenosis, that is, whether it is rheumatic or sclerotic in origin, is unsolved and probably insoluble so long as our knowledge regarding the causal factors themselves is so deficient.

ROSENBAUM

**Douglas, D. M.: Mitral Regurgitation with Mobile Valve Cusp.** Brit. M. J. 1: 191 (Jan. 26, 1957.

On the basis of 3 patients, the author points out an exception to the rule that a loud first sound in the mitral area rules against predominant mitral regurgitation. In 3 patients the cusp at the margin seemed to be held open by shortened chordae tendineae but the valve curtain, especially that of the anterior cusp, was still mobile. Results of valvulotomy were not optimal in these patients.

MCKUSICK

## VASCULAR DISEASES

**Herrmann, J. B., and Gruhn, J. G.: Lymphangiosarcoma Secondary to Chronic Lymphedema.** Surg., Gynec. & Obst. 105: 665 (Dec.), 1957.

Chronic lymphedema of the arm following mastectomy for cancer is thought to predispose to the development of angiosarcoma according to this review of the 21 such case reports plus 5 newly described ones. The tumor appears on an average of 10.5 years postoperatively and is seen as purplish nodules just above or below the elbow. It usually resists roentgen therapy or surgical removal, and pulmonary metastases occur in most patients within a year after recognition of the disease. The histologic resemblance to Kaposi's sarcoma is mentioned; and while this malignancy is seen occasionally in legs that are usually not swollen, the occurrence of lymphangiosarcoma in edematous legs is quite rare (2 reported cases).

ROGERS

**Stuart, K. L., and Bras, G.: Veno-Occlusive Disease of the Liver.** Quart. J. Med. 26: 301 (July), 1957.

The clinical and pathological characteristics of a recently recognized syndrome, veno-occlusive disease of the liver, are described in 84 Jamaican patients. In the acute stage, hepatomegaly and ascites develop suddenly, usually in children between 1 and 6 years. In the subacute stage, there is persistent hepatomegaly; the chronic stage resembles clinically cirrhosis due to other causes. The primary lesion in the acute stage is widespread occlusion of the smaller and medium-sized branches of the hepatic veins with sinusoidal congestion and pressure necrosis of parenchymal cells around central veins. In some cases, this is followed by nonportal cirrhosis originating around the central veins. Forty-eight per cent showed complete recovery; 19 per cent died in the acute phase; the rest entered a chronic phase. The death rate is highest in infants under 1 year and in adults. Although the etiology remains obscure, it is possible that the syndrome is produced by plant toxins.

KURLAND

**Carter, A. B.: The Immediate Treatment of Cerebral Embolism.** Quart. J. Med. 26: 335 (July), 1957.

This study compares the results of therapeutic methods in 60 consecutive patients with cerebral embolism divided into 4 groups. At the end of 3 months there was no significant difference between the control group of patients (1953) and patients treated by repeated stellate block (1952). There was no difference between treatment with anticoagulants and stellate block (1954) and that by anticoagulants alone (1955) but both groups treated with anticoagulants were superior in results to the other 2. No ill effects from anticoagulants were demonstrated in examination of the infarcted area of brain in fatal cases.

KURLAND

**Burstein, J., Lindstrom, B., and Wasastjerna, C.: Aortic Arch Syndromes: A Survey of Five Cases.** Acta med. scandinav. 157: 365 (June), 1957.

Five patients with aortic arch syndromes char-

acterized by obliteration of 1 or more of the large arteries originating from the aortic arch are presented. Four of them were verified arteriographically. In 3 patients the etiology was probably atheromatosis, in 1 either arteritis or atheromatosis and in 1 rheumatic arteritis. In 2 patients the course of the disease was dominated periodically by coronary symptoms and myocardial infarctions, which were probably due to the basic vascular disease producing the aortic arch syndrome. The administration of anticoagulants seemed to be beneficial in 2 patients. ACTH, cortisone, and antibiotics were ineffective therapeutic agents in patients with the aortic arch syndrome of atheromatous origin. Androgens are contraindicated but estrogens may be worthy of a trial. The authors believe that the term pulseless disease is inadequate. Aortic arch syndrome seems more appropriate and comprises all the different pathologic processes that may produce obliteration of large arteries originating from the aortic arch. The etiology, when known, should be indicated.

BROTHERS

**Torma, T., and Troupp, H.: Thrombosis of the Internal Carotid Artery.** Acta med. scandinav. 158: 89 (Aug. 13), 1957.

This paper represents a study of 31 patients with thrombosis of the internal carotid artery diagnosed by angiography. Twenty-four patients were men and 7 women. The lesion was seen most frequently in individuals 30 to 60 years of age, with 28 patients falling in this age group. Nineteen patients had thrombosis on the left side and 12 on the right. In 24 patients the thrombosis was situated at or immediately above the bifurcation of the common carotid and in 7 at the level of the carotid siphon. The chief etiologic factor was assumed to be arteriosclerosis. Patients were grouped as acute, subacute, and chronic depending on the clinical picture. In the 8 acute patients there was sudden onset without premonitory signs, severe headache, motor and speech disturbances, and clouded sensorium. Eighteen patients were classified as subacute and had experienced fleeting symptoms for some time, such as headache, transient weakness of extremities, and paresthesias, and then an acute exacerbation with symptoms of the acute group. In the 5 patients comprising the chronic group, the chief symptoms were headache, motor and speech disturbances, sensory disturbances, mental changes, epileptic fits, and ocular symptoms. Angiography was considered to be the most important single diagnostic aid. Special films demonstrating the needle to be in the lumen of the vessel were necessary if diagnostic errors were to be avoided. Angiography was usually done percutaneously. Electroencepholographic changes consisted of general slowing and pathologic delta and theta waves; no pathognomonic changes were observed. Therapy was aimed at preventing extension of the thrombus and abolishing reflex spasm in cerebral vessels through the use of anticoagulants and vasodilators. In 2 patients cervical sympathectomy was performed with no apparent benefit; 5 patients had stellate ganglion block without definite beneficial results. The prognosis was generally poor. Only 3 patients recovered; 13 improved but had residual neurologic deficits, 8 were unimproved, 1 was worse, and 6 died.

BROTHERS

## OTHER SUBJECTS

**Andrews, E. C., Jr.: Five Cases of an Undescribed Form of Pulmonary Interstitial Fibrosis Caused by Obstruction of the Pulmonary Veins.** Bull. Johns Hopkins Hosp. 100: 28 (Jan.), 1957.

There is a surprising dearth of previous reports of the association between pulmonary venous obstruction and interstitial fibrosis of the lung. Indeed, there is a paucity of investigations of pulmonary venous obstruction. In the first case there was a left atrial myxoma, and in the second a ball valve thrombus of the left atrium, large enough to interfere with pulmonary venous flow. In 2 further cases mediastinal collagenosis was responsible for constriction of the pulmonary veins. In the fifth case, a 3-year-old child, there was congenital stenosis of the pulmonary veins. Histologically there were some parallels to the reported findings in "idopathic pulmonary hemosiderosis." Possibly the pulmonary veins should be examined with particular care in cases of the latter type.

MCKUSICK

**Behrman, S., and Knight, G.: Carotid Sinus Epilepsy and Its Treatment by Denervation.** Brit. M. J. 2: 1522 (Dec. 29), 1956.

In a few individuals unconsciousness was precipitated by digital pressure on the carotid sinuses, yet no change in cerebral blood flow was demonstrable. Transient delta rhythm appeared. The authors suggest that this represents a sensorily precipitated epilepsy. This is a fourth mechanism for syncope induced by carotid sinus pressure, the others being cerebral ischemia, cardiac slowing, and drop in blood pressure through fall in peripheral resistance.

MCKUSICK

**Daley, R.: The Autonomic Nervous System in Its Relation to Some Forms of Heart and Lung Disease. I. Heart Disease.** Brit. M. J. 2: 173 (July 27), 1957.

In a general discussion the author considers various aspects of the complicated role of the autonomic nervous supply to the heart in some diseases of that organ. The nature of cardiac pain is discussed. The metabolic changes consequent to myocardial infarction are stressed. A case is described of a patient with a variety of autonomic disturbances associated with attacks of angina pectoris; these were best explained by central radiation within the spinal cord. The "shoulder-arm" syndrome and excessive flatulence sometimes associated with coronary disease are considered as probable concomitant autonomic phenomena. It is pointed out that the association between cardiac pain, gallbladder disease, and hiatus hernia may be more than a reduction of pain threshold and that either condition may cause a reduction in coronary arterial blood flow. In regard to operations designed to revascularize ischemic hearts the author believes that the evidence indicates that pain is diminished because sympathetic afferent pain fibers are destroyed. He also illustrates that upper dorsal sympathectomy and direct denervation of the heart may well have a place in uncontrollable atrial fibrillation and sometimes in repeated Stokes-Adams attacks.

SAGALL

## REVIEWS IN CARDIOVASCULAR DISEASE

**Muehrcke, R. C., Kark, R. M., Pirani, C. L., and Pollak, V. E.: Lupus Nephritis: A Clinical and Pathological Study Based on Renal Biopsies.** Medicine **36**: 1 (Feb.), 1957.

**Keefer, C. S.: Pyelonephritis. Its Natural History and Course.** (Thayer Lecture I for 1956.) Bull. Johns Hopkins Hosp. **100**: 107 (March), 1957.

**Kupfer, S.: The Place of Dialysis Procedures in Clinical Management.** Am. J. Med. **22**: 511 April), 1957.

**Lawry, E. Y., Mann, G. V., Peterson, A. Wysocki, A. P., O'Connell, R., and Stare, F. J.: Cholesterol and Beta Lipoproteins in the Serums of Americans. Well Persons and Those with Coronary Heart Disease.** Am. J. Med. **22**: 605 (April), 1957.

**Verstraete, M., and Vandenbroucke, J.: Deficient Thromboplastin Formation in Man.** Am. J. Med. **22**: 624 (April), 1957.

**Gross, R. E.: Present Status of Surgery for Treatment of Congenital Cardiovascular Malformations.** Bull. New York Acad. Med. **33**: 299 (May), 1957.

**Fisher, C. M.: Cerebral Thromboangiitis Obliterans.** Medicine **36**: 169 (May), 1957.

**Samet, P., Fritts, H. W., Jr., Fishman, A. P., and Cournand, A.: The Blood Volume in Heart Disease.** Medicine **36**: 211 (May), 1957.

**Selzer, A., Willett, F. M., McCaughey, D. , and Feichtmeir, T.: Uses of Cardiac Catheterization in Acquired Heart Disease.** New England J. Med. **257**: 66, 121 (July 11, 18), 19 .

**Yudkin, J.: Diet and Coronary Thrombosis. Hypothesis and Fact.** Lancet **2**: 155 (July 27 , 1957.

**James, L. S.: Changes in the Heart and Lungs at Birth.** J. Pediat. **51**: 95 (July), 1957.

**Hall, V.: The Protoplasmic Basis of Glomerular Ultrafiltration.** Am. Heart J. **54**: 1 (July , 1957.

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# AMERICAN HEART ASSOCIATION, INC.

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## AHA SCIENTIFIC SESSIONS OFFER PROGRAM FOR CLINICIANS

An all-day Program for Clinicians, including symposia on "Congenital Heart Disease," "Treatment of Intravascular Clotting," and "Peripheral Arterial Insufficiency," will be among the highlights of the American Heart Association's 31st Annual Scientific Sessions in San Francisco, October 24-26. The Program for Clinicians, scheduled for Friday, October 24, is sponsored by the Council on Clinical Cardiology.

In addition to the symposia, the clinicians will discuss such special subjects as "Clinical Evaluation of Chlorothiazide," "Traumatic Heart Disease," and "The 'Tough Case' of Bacterial Endocarditis." A panel discussion, "What's New in Arrhythmias," will also be held. It is expected that many practicing physicians from the Rocky Mountain and Pacific coast areas will attend these sessions, which have been classified by the American Academy of General Practice as acceptable for credit for Academy members.

Other features of this year's Scientific Sessions include joint programs with the American Society for the Study of Arteriosclerosis and the Microcirculatory Conference. This year for the first time, the American Society for the Study of Arteriosclerosis is holding its Annual Meeting to coincide with the AHA Scientific Sessions.

Following is a tentative schedule for the three-day meeting. All Scientific Sessions will be held at San Francisco's Civic Center.

***Friday, October 24***

Morning: A session on genetics, to be presented jointly by the AHA and the American Society for the Study of Arteriosclerosis; Sessions under sponsorship of the Association's Councils on Circulation and Cardiovascular Surgery.

Afternoon: Session sponsored by the Council on Rheumatic Fever and Congenital Heart Disease; Symposium to be conducted jointly by the Association's Council on Circulation and the Microcirculatory Conference.

Evening: Session on "Instrumental Study of the Heart and Circulation."

***Saturday, October 25***

Morning: Session on Applied Cardiovascular Research; Lewis A. Conner Memorial Lecture by John H. Gibbon, Jr., M.D., Professor of Surgery, Jefferson Medical College, Philadelphia, on "Maintenance of Cardio-Respiratory Functions by Extracorporeal Circulation;" George E. Brown Memorial Lec-

## AHA FELLOWSHIP APPLICATIONS DEADLINE IS SEPTEMBER 15

September 15 is the deadline for submitting applications for Research Fellowships and Established Investigatorships to be awarded by the Association for the fiscal year beginning July 1, 1959. Applications for grants-in-aid during the same period must be received by the Association by November 1, 1958.

All applications must be made on forms available from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N.Y. The following awards are involved: Advanced Research Fellowships, stipends range from $4,600 to $6,500 annually; Established Investigatorships, $6,500 to $8,500, plus dependency allowances; Research Fellowships, $3,800 to $5,700. Classification as Research or Advanced Research Fellow is at the discretion of the Association's Research Committee.

ture by Lewis Thomas, M.D., Professor and Chairman, Department of Medicine, New York University College of Medicine, on the "Role of Hypersensitivity in Cardiovascular Disease;" Presentation of the Albert Lasker Award of the American Heart Association for distinguished achievement in cardiovascular research.

Afternoon: Panels on "Emotional and Endocrine Aspects of Cardiovascular Disease" and "Effects of Hemodynamics and Vascular Injury," to be presented jointly with the American Society for the Study of Arteriosclerosis.

***Sunday, October 26***

Morning: Simultaneous sessions to be conducted by the Councils on Clinical Cardiology, High Blood Pressure Research, and Basic Science.

Afternoon: A special program arranged by the Council on Community Service and Education, "Rewards of Research," designed to interest laymen as well as physicians; Sessions on Rheumatic Fever Secondary Prevention Programs, sponsored jointly by the Councils on Rheumatic Fever and Congenital Heart Disease and Community Service and Education.

The Association's Annual Dinner is scheduled for Sunday evening at the Fairmont Hotel.

Concurrent with the Scientific Sessions, a medical film program will be shown each day. As in previous years, a section of scientific and industrial exhibits will also be provided.

***Early Registration Urged***

As an inducement to early registration all physicians who register prior to the Scientific Sessions will receive for the first time this year an advance complimentary copy of the program booklet containing abstracts of the proceedings. At the meeting, these abstract programs will be sold for $1.00. Registration and hotel accommodation forms are now available from the Association.

***Annual Meeting of Assembly***

The Annual Meeting of the Assembly to review national policies and activities of the Association will be held on Monday, October 27 and Tuesday, October 28 at the Hotel Fairmont.

Six Assembly Panels will be in session on Monday to discuss the following subjects: Research; Fund Raising and Public Relations; Relationships and Responsibilities between National, State and Local Heart Associations; Community Service-Screening and Case Finding Programs; The Physician's Continuous Self-Education; and Membership.

The general session of the Assembly meets on Tuesday morning to review Panel recommendations and elect officers and Board members of the Association.

## ARTERIOSCLEROSIS SOCIETY SCHEDULES SCIENTIFIC SESSIONS

Forty-four papers will be presented at four scientific sessions to be held by the American Society for the Study of Arteriosclerosis at its Annual Meeting in San Francisco, October 22-26. The Society has scheduled its meeting this year to coincide with the American Heart Association's Scientific Sessions in San Francisco, October 24-26. Several programs of joint interest have been planned.

The Society's meeting opens with all-day workshop sessions conducted by the Committee on Lesions on Wednesday and Thursday, October 22-23 at the Hotel Whitcomb. On Friday morning, October 24, a session on genetic factors will be held jointly with the American Heart Association at the Civic Center.

The Society's Scientific Sessions begin Friday afternoon and continue on Saturday morning at the Hotel Whitcomb. Additional scientific sessions will be held throughout Sunday at the Civic Center. The G. Lyman Duff Memorial Lecture by George E. Wakerlin, M.D., Medical Director of the American Heart Association on "Arteriosclerosis and the Program of the American Heart Association," will be given at the society's luncheon on Saturday. Panels on arteriosclerosis will be presented jointly with the American Heart Association on Saturday afternoon at the Civic Center. R. Gordon Gould, Ph. D., Presi-

d t of the American Society for the Study of A teriosclerosis, will address the scientific s sion on Sunday afternoon.

## SYMPOSIA AND ROUND TABLES AT 3rd WORLD CONGRESS OF CARDIOLOGY

An advance registration of over 2,500 physici ns from all parts of the world was reported fo the Third World Congress of Cardiology in Brussels, September 14-20 at the time this issue went to press. Many more are expected to hear approximately 500 papers which will be presented daily from 9:00 to 11:00 A.M. and from 2:00 to 6:00 P.M.

The Office of the Congress Secretary at Brussels University, 51 Boulevard Franklin Roosevelt, will open at 9:00 A.M. on Saturday, September 13. All those attending the Congress are advised to report to this office immediately after arrival to check on accommodations and attendance at the various meetings and functions.

At 2:00 P.M. on Sunday, September 14, the technical exhibits will open officially, and at 5:00 P.M. opening ceremonies for the Congress will be held in the main room of the Palais des Beaux Arts, Rue Ravenstein. At 8:00 P.M. a welcoming reception will be held at the Musees des Arts du Cinquantenaire, Avenue des Nerviens.

Symposia are scheduled for each morning of the Congress and round table sessions almost every afternoon. On Monday, September 15th, subjects will include cardiac electrophysiology, coronary circulation, rheumatic fever, surgery for acquired heart diseases and angiocardiography.

On the 16th, subjects will include physiology of the cardiovascular regulation, normal limits and functional modifications of the ECG, and phonocardiography. At 11:15 A.M. there will be a general conference in which Dr. Paul D. White of Boston will participate.

On the 17th, subjects will include automatism of the heart, peripheral circulation, pulmonary function in mitral stenosis and diagnosis of coronary diseases. On the 18th, subjects will include collagen diseases and "social cardiology." On the 19th, topics will include cardiac insufficiency, arteriosclerosis, surgery for congenital heart diseases and geographic epidemiology. At 11:00 A.M. there will be a lecture by the winner of the Prize of the Belgian Society of Cardiology. On the 20th, topics will include subacute bacterial endocarditis and hypertension.

In addition to technical exhibits there will be scientific exhibits and films on cardiology. A joint exhibit showing the complementary efforts of the American Heart Association and the National Heart Institute during the past decade will be on view.

Until the opening of the Congress, inquiries should be addressed to the Secretary, Fr. van Dooren, at 80 Rue Mercelis, Brussels.

## SCIENTIFIC PROGRAM TO OPEN NEW CV RESEARCH INSTITUTE IN SAN FRANCISCO

A special scientific program to mark the opening of its new Cardiovascular Research Institute will be presented by the University of California Medical Center in San Francisco, October 23, preceding the AHA Scientific Sessions.

Speakers on the program include Sir George Pickering, Regius Professor of Medicine, University of Oxford, England; Dr. I. Lyon Chaikoff, Professor of Physiology, University of California, Berkeley; Dr. Malcolm McIlroy, First Assistant, Institute of Cardiology, London; and Dr. Julius H. Comroe, Jr., Director of the new Cardiovascular Research Institute.

Those wishing to attend may write for tickets at the University of California Medical Center, San Francisco 22, Calif.

## NEW BOOKLET ON RESEARCH CAREERS

A new booklet, "Decision for Research," has been issued by the Association as a follow-up to the educational television series of the same name presented by NBC-TV and AHA to stimulate student interest in research careers. The booklet, prepared and published with assistance from E. R. Squibb and Sons, a division of Olin Mathieson Chemical Corpo-

ration, gives additional information about planning for a research career. It is obtainable free of charge from local Heart Associations or from the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

## MEETINGS CALENDAR

August 24-29: Congress of Physical Medicine and Rehabilitation, Philadelphia. Frances Baker, 1 Tilton Street, San Mateo, Calif.

October 6-10: American College of Surgeons, Chicago. Michael L. Mason, 40 E. Erie Street, Chicago 11, Ill.

October 13-15: Association of American Medical Colleges, Swampscott, Mass. Mrs. Lotus R. Barnes, 2530 Ridge Ave., Evanston, Ill.

October 20-23: American Academy of Pediatries, Chicago. E. H. Christopherson, 1801 Hinman Avenue, Evanston, Ill.

**October 24-28: American Heart Association Annual Meeting and Scientific Sessions, San Francisco. American Heart Association, 44 East 23rd Street, New York 10, N.Y.**

October 27-31: American Public Health Association, St. Louis. Berwyn F. Mattison, 1790 Broadway, New York 19, N.Y.

October 31-Nov. 1: Central Society for Clinical Research, Chicago. A. S. Weisburger, 2[illegible] Adelbert Road, Cleveland 6, Ohio

November 6-8: Gerontological Society, Inc., 1[illegible] Annual Scientific Meeting. Philadelphia. Jose[illegible] T. Freeman, 1530 Locust Street, Philadelphia [illegible], Pa.

November 14-15: First annual Symposium [illegible] Cinefluorography, Strong Memorial Hospit[illegible] Rochester, N.Y. George H. Ramsey, Depa[illegible] ment of Radiology, Strong Memorial Hospit[illegible] Rochester 20, N.Y.

## ABROAD

**September 14-21: Third World Congress of Cardiology, Brussels. F. Van Dooren, 80 R[illegible] Mercelis, Brussels, Belgium.**

September 22-28: 16th International Congress of History of Medicine, Montpellier, France. Louis Dulieu, Montpellier, (Herault) France.

September 24-28: Third International Congress of Angiology, San Remo, Italy. M. Comel, Clinica Dermatologica, Università di Pisa, Italy.

November 30-December 3: Fourth Latin-American Congress of Angiology, Santiago, Chile. Juan Borzone Galvez, Cassila 10256, Santiago, Chile.

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